THE TURKISH JOURNAL OF PEDIATRICS

PUBLISHED BY
Turkish National Pediatric Society,
Hacettepe University
Institute of Child Health and
The Turkish and International
Children's Center

PRINTED IN
Meteksan Anonim Şirketi, Ankara

ISSN 0010-0161

This publication is included in the abstracting and indexing coverage of BIOSIS Previews, CAB Abstracts (Abstracts on Hygiene and Communicable Diseases, Public Health Bulletin, Tropical Diseases Bulletin), EMBASE/Excerpta Medica, IBIDS (International Bibliographic Information on Dietary Supplements), MEDLINE/ Index Medicus, MICROMEDEX for Health Care Series, Research Alert Direct (ISI), Science Citation Index Expanded (ISI), SERLINE and Turkish Medical Index.

EDITORIAL OFFICE
Prof. Dr. Turgay Coşkun
Editor
The Turkish Journal of Pediatrics
P.K. 66, Samanpazarı
06240 Ankara, Turkey
Fax: 90 (312) 324 32 84

SUBSCRIPTION ADDRESS
Prof. Dr. A. Murat Tuncer
Director
Hacettepe University
Institute of Child Health
06100 Ankara, Turkey
Fax: 90 (312) 324 32 84

THE TURKISH JOURNAL OF PEDIATRICS

VOLUME: 42 NUMBER: 1 JANUARY - MARCH 2000

CONTENTS

Better childhood in the next millennium*

Perla D. Santos Ocampo

Dualan Distinguished Professor and Chancellor, University of the Philippines, Manila, Taft Avenue, Manila, Philippines

"You are a child of the universe. You have a right to be here."
Desiderata

We live today in interesting times. In less than four months, the third millennium and the 21st century will be upon us. The countdown will now be better understood if this is expressed in days, only 98 altogether, less than a hundred. As our ancestors and rural folk will say in more picturesque terms, we will hear the cock crow only 98 more times, we will witness the sun rise and set in less than a hundred days, and the dawn of the new millenium will be upon us. Our concern today is to achieve better childhood in the next millenium. Note that the task given to me is not merely child health but childhood, denoting a definitely more holistic and encompassing term.

The past decade has been characterized by very rapid changes-it was sometimes necessary to hold one's breath as one witnessed the swift transformation of much of our environment including our buildings, communications, plants, food, drugs and vaccines, garbage disposal and transportation due to technological advances. Definitely we are at the threshold of a new millenium. We expect our world in the first decades of the 21st century will be very different from what we have today. Undeniably, the social, economic and ecological landscapes, the communities, the household, and the family will be different. Population movements will drastically change the demographic profile of cities and villages. A different culture will evolve as new technology impacts on organizations and processes. The health care environment will be different as this is most sensitive to the swirling storm of change going on. As people, especially the vulnerable, increasingly become incapable of responding to these changes and harnessing them in their service, there will be new illnesses, new problems, new manifestations of stresses and conflict. As we continue to grapple with the diseases of antiquity still with us, such as tuberculosis and pneumonia, new diseases will emerge, many of which are caused by changing life styles and the deteriorating environment.

But more tragic is the increasing difference between developed and developing countries. The gaps between the health status of the rich and the poor, the technology status between the North and South, the resources between the "haves" and the "have not" continue to be as wide or wider. The 10/90 disequilibrium in all aspects of life and survival, not only in health research, will persist or even worsen during the first decade of this coming century.

Undeniably, the 20th century has brought much improvement in child health in many parts of the world, but is well recognized that certain problems are perpetuated while new concerns emerge.

On Location, In Asia

We are in Asia: Krygyzstan and other Turkish speaking countries are in Asia. We are here with the Turkish National Pediatric Society through the magnificent and effective leadership of Professor İhsan Doğramacı, a brillant and intensely patriotic Turk whose innovativeness and resourcefulness has allowed the International Pediatric Association (IPA) to reach out to this and many other areas of the world. Although Turkey straddles the West and East, Turkey can readily lay claim to be Asian. The richness of its civilization emanates from this remarkable blending. These remarks presage my subsequent statemenets.

New Horizons Affecting Childhood
The Spectrum of Child Health Issues

When this assignment was given to me, my first impulse was to pray for the sagacity of a Socrates or the prescience of a Nostradamus, and the omniscience of an oracle to look or just to peep into the future. I do not feel that may

* Presented during the 5th Regional Congress of Pediatric Societies of Turkish Speaking Countries, 25-28 September 1999, Bishkek, Kyrgysztan.

prayers were granted but I can never, never deny any requests from my esteemed and beloved Turkish friends. So here goes, with the help of a number of authoritative readings.

The spectrum of child health issues will range from problems resulting from persistent underdevelopment and poverty to transitional diseases to those emanating as a consequence of advanced development. With advances in science and technology, particularly, information technology, it is usually expected that there will be a shift in the pattern of the disease burden. It is projected that non-communicable diseases and injuries will assume greater prominence. However, with certain determinants, the predicted shift in the pattern of disease burden may not occur at all, particularly in childhood, thus defying predictions by scientific and futuristic pundits.

In most developing countries, a double burden of disease thus exists. The approach differs widely. The burden of diseases of developing countries is highly determined by poverty. Fortunately, these problems can be alleviated by a number of well studied programs that can be put in place. The epidemiological transition points to a diversity of problems which must be addressed.

Developing			Transition		Developed	
	Infectious Diseases		Injuries	Genetic	Psychosocial	
Malnutrition, Poor reproductive health	Old/ Reemerging	New/ Emerging	Accidents	Problems	Problems	Socio-Political Problems
High childhood maternal morbidity mortality	Diarrheas Respiratory problems Measles Malaria Parasitic diseases	HIV/AIDS Ebola Other viruses	Violence Abuse Child labor	Congenital malformations Hereditary, familial diseases	Adolescent health problems Mental illness Substance abuse Teenage pregnancies Youth violence	Displaced children Abandoned children Refugee children Child soldiers

The Determinants of the Millennium Pattern of Disease Burden

To poverty has long been attributed many child health problems. But recently, this has been further exacerbated by the on going economic crisis, particularly in Asia, where abandoned children are now known as IMF (International Monetary Fund) children or orphans, abandoned by parents whose busineses have gone bankrupt.

It is well recognized that globalization in countries ill prepared for a borderless world has aggravated the economic situation and has a deleterious influence on children, the most vulnerable sector of society. Marginalization of this sector will be exacerbated by the economic regression.

Shrinking currencies have resulted in a financial volatility which will stretch every currency to its limit to cover the expanding cost of health care. Undoubtedly, whatever funds are available for health care will buy less and less. This gloomy situation will sustain the existing inefficiency, inequity and inaccessibility of health care.

The global village has led to a borderless world facilitating a free exchange between countries not only of knowledge, science, technology and ideas but also of peoples, market goods and even of psychoactive drugs, tobacco and microbial agents.

In addition, the globalization of western cultural norms and lifestyles imposes challenges on the integrity of native cultures and anomie.

HIV/AIDS has become a major problem in Africa, Asia and Latin America. The risk of orphanhood due to AIDS is reaching terrifying magnitudes. By 2010, it has been predicted that 40 million children in Africa and Latin Ameria will have lost one or both parents due to the pandemic. These children, deprived of parental support and care, will eventually be forced into the streets, into child labor, will be deprived of a nurturing home and schooling and many eventually succcumb to HIV/AIDS themselves.

Rapid introduction of new technology without the corresponding social preparation has contributed to increase in injuries. Childhood injuries are among the major health problems of western industrialized countries, but are increasing quite rapidly in developing countries as well.

Continuing wars and hostilities in many parts of the world have perpetuated the horrendous plight of children caught in the crossfire and violence resulting in displacement from families, loss of parents, injuries (both physical and psychological), and death. In addition to these, man-made calamities, natural disasters of more horrible dimensions are occurring almost daily in many parts of the world. The loss of social support among displaced families, often as a result of war or political and natural catastrophes, takes a tremendous toll on the well being of our children. Displacement and economic losses put a lot of stress on the capacity of the family to care for children. It disables families from performing the basic role of care giving. Rapid population movements stretch the available community support to the limit and render traditions which are communities' constant sources of coping incapable of providing such support.

The apparent lack of political will in most countries leads to inadequate budgetary alocations for health, inefficient health organization and management, inappropriate and inadequate health manpower, and an ineffective health information system, all contributing to a high morbidity and mortality. All this, in spite of health care being a fundamental human right.

A pervasive breakdown in traditional family life, values and culture during this critical transition from the 20th to the 21st century creates a deleterious effect on the child's survival and development. Swiftly disappearing is the extended family of yesteryears which provided much suport to children exposed to parental problems and counteracted the detrimental effects of dysfunctional nuclear families. There is now an alarming change in the sociology of the family characterized by single parent or no parent households. Parents have to work away from the home to eke out a living.

Access to pernicious media, especially television violence, lewd shows and pornographic printed material has exposed both adults and children to detrimental stimuli which foster violence, abuse, sexual adolescent health problems, perversions, tobacco smoking and dietary fads.

Urbanization, under the guise of modernization, has brought with it both advantages and disadvantages. In developing countries, flight into the cities has resulted in urban blight as witnessed by slums where families live on the sidewalks, in carts, in cardboard hovels, along perilous river banks and railroad tracks, under extremely unhygienic and unsanitary situations, imposing a heavy load on already inadequate social, environmental and educational services. Much has been said about the deleterious effects on the child of our environmental degradation. Environmental risks continue to emerge and worsen, such as exposure to lead, dioxins and other pollutants.

In spite of modern age science and technology an knowledge and information, harmful traditional practices of the past affecting children will still persist. Girl children are particularly affected. Among these horrendous practices are fetocide, infanticide, female genital mutilation, and unequal access to health care, psychosocial stimulation and educational opportunities. Girl children are expected to do more domestic work and are forced into early marriages and pregnancies and even prostitution.

All these lead to frequent illnesses, poor growth and development, abuse, neglect, violence, and other psychosocial and emotional problems.

In most developing countries, more than 50 percent of deaths will still be accounted for by acute respiratory infections, diarrhea, measles, malaria, and malnutrition, with one-third of infant deaths due to neonatal deaths.

Achieving the Mission

As we look back on what has been done to improve the status of children at this moment in time, two documents come to mind, the Alma Ata declaration of 1978 and the Convention on the Rights of the Child in 1989, followed by the World Summit for Children in 1990. These documents, forged by caring, compassionate and competent world leaders, are invaluable and infallible testimony to the determination of mankind to improve the state of well being and quality of life of people and children everywhere.

Other international initiatives oriented towards better child health are:

- The Geneva Declaration on The Rights of the Child, 1954
- The Universal Declaration on The Rights of the Child, 1959
- The International Covenant on Civil and Political Rights, 1966

Selected health-for-all (HFA) indicators	1975			1997			2025			HFA targets
	Average	Max.	Min.	Average	Max.	Min.	Average	Max.	Min.	
Life expectancy at birth (years)	46	64	35	53	72	38	65	77	51	> 60
Infant mortality rate (per 1000 live births)	125	197	47	89	169	16	47	99	7	< 50
Under-5 mortality rate	200	294	51	139	251	16	66	139	6	< 70

• The UN Convention on the Elimination of All Forms of Discrimination Against Women, 1979

• The World Conference on Education for All, 1990

• The International Conference on Nutrition, 1992

• The International Conference on Population and Development, 1994

• The Fourth World Conference on Women, 1995

To attain the goals of these international statutes, certain interventions are to be focused on. In the next few minutes (pages), I shall touch upon some measures which have been proven in the past decades to contribute to the improvement of the quality of life of children and are predicted to continue to be able to ensure better childhood. The pediatrician is thus encouraged to support these measures individually or through groups and organizations.

Continued Implementation of the Alma-Ata declaration of 12 September 1978

Over-all survival prospects for the world's population have improved with the political commitment of member states and with the development of health systems based on primary health care. However, issues of inequalities in health status and health care continue to persist, as these have not been adequately or effectively addressed during these past two decades. substantial progress has been achieved but definitely only to a partial extent. Examples are:

In the developing world	1990	1994
Access to safe water	61%	75%
Access to sanitation services	36%	34%

Selected health-for-all (HFA) indicators are hereby presented as obtained from The World Health Report, 1998, depicting progress from 1975 to 1997 and predicting what it would be in 2025.

Enforcement of the Convention on the Rights of the Child

The World Summit for Children brought into force by all nations of the world the articles of the Convention on the Rights of the Child.

The World Health Report, 1998, "Life in the 21st Century: A vision for all" by the World Health Organization estimates how the following goals fared for 1995.

One hundred and two member states with a total population of 3.4 billion (60% of the global population) had achieved:

• In 1995, an infant mortality rate of below 50 per 1000 live births.

• An under-5 mortality rate of below 0 per 1000 live births.

• In 1996, immunization coverage of infants was

nearly 90% for BCG
nearly 80% for DPT3, measles and poliomyelitis
almost 50% for tetanus toxoid for pregnant women

Development and Maintenance of Dynamic and Effective Health Systems

The biomedical model of health systems predominated until the Declaration of Alma-Ata in 1978. This model emphasized the medical sector with training of doctors and nurses, creation of infrastructures such as hospitals, and distribution of medicines. The limitations of the biomedical model became apparent and, following the Declaration of Alma-Ata, new paradigms led to increasingly credible options worldwide.

The goals for health systems in countries can be stated in many ways, but the World Health Report 1999 has summed it up in broad terms as follows:

- improving health status
- reducing health inequalities
- enhancing responsiveness to legitimate expectations
- increasing efficiency
- protecting individual, families and communities from financial loss

Sustained Data Collection, Monitoring and Evaluation

Reports and databases serve as alert-systems to call attention to a widening gap in health status

and to gather data which would be most helpful in policy decisions and interventions. Any program seriously implemented merits constant monitoring and a periodic evaluation to ensure its effectiveness and success. These interventions are particularly important in dealing with programs for better childhod.

Advocacy, Political Commitment and Family and Community Participation

Most vital is broadening support for childrens' issues. Political commitment by leaders easily breaks down many of the barriers obstructing better childhood. It is necessary to acknowledge the importance of the family structure. Although empowerment is to be intensified for women and children, one must also speak of parent empowerment and community empowerment.

Public health policies must be well thought out to address the community's health concerns. Legislation is vital in support of health measures and in the generation of resources to implement such interventions. John Ruskin (1819-1900) showed us the way by stating even then, a full century before our international statutes were formulated: "I hold it indisputable, that the first duty of a State is to see that every child born therein shall be well housed, clothed, fed and educated".

Universalism has been a buzz world for health care for many of our more advanced countries More and more, it is now being realized that the classic form of universalism is constrained by limits of resources and government. A new definition has evolved for what is now termed as a new universalism that recognizes limits of government but retains the government's responsibility for leadership and finance of health care.

Strengthening Capacities of Training Institutions to Reorient Curricula to Meet Changing Needs

It is necessary to keep in mind that with the changing health-related agendas brought about by megatrends, academic institutions should continue reorienting their curricula to produce relevant and responsive health professionals with the competencies, skills commitment and compassion to address the double burden of childhood problems.

Harnessing Information Technology

The potential of information technology is limitless. Its applications for education, training and research are inexhaustible. New communication technology has facilitated globalization and will continue to be one of the major forces responsible for the irreversible trend toward globalization.

New technology has transformed the viewer or listener from a passive audience to an active (media/technology) user or participant. Virtual reality will continue to be most exciting and promising but the most recent role is that of extending human intellectual capacity. It is not merely artificial intelligence but intelligence amplification which enables computers to do things that the human mind cannot do.

Telemedicine will address a tremendous number of concerns and will facilitate both health education and continuing medical education.

Better Education, Literacy

Communication technology as learning delivery channels will facilitate integration or coordination of formal and non-formal education, innovative or non-traditional learning approaches and open learning or distance education.

Health eduation has been a well proven effective intervention strategy in improving health practices and customs in the prevention of disease and in the care of the sick. In addition to trimedia, information technology should be harnessed to facilitate access to new health information by both the public and health care providers.

Despite the dizzying pace of change, we continue to believe in the same fundamental principle that knowledge means both survival and power.

Networking, Linkages, Partnerships

Continued linkages with the following United Nations organizations will have to be encouraged at different levels: UNICEF, WHO, UNFPA, Food and Agriculture Organization, CIOMS, UNECSO, ILO, and UNAIDS.

Other partners include governmental and non-governmental organizations, civil society and the private sector.

Research and Development

The creation of new knowledge has always been the basis of policy changes. It has provided clearer evidence, especially for the economic benefits of improving health. There is a need to concentrate resources for research on poor

countries or on vulnerable groups without alternative sources of funds to be able to amplify impact and make a difference.

Health knowledge according to the Council on Health Research for Development is constituted by three broad steps:

- the generation of knowledge through research
- the optimization of knowledge
- the mobility and utility of knowledge

It is necessary to bridge the 10/90 gap as described by the Global Forum for Health Research on Promoting Research to Improve the Health of Poor People.

Focus on children's problems should be a priority for governments. It should be recognized that funds given for research is not "spending" but "investing" to bring progress to our country and people. It is to be recognized that there are increasingly fluid borders between health/ biomedical, pharmaceutical nutrition, and agricultural research.

Molecular and Social Sciences

The causes of malnutrition have always been enumerated as economic, social, cultural, and political. Agricultural factors should be included and given the prominence they deserve from the beginning. The emphasis in recent decades is on agricultural biotechnology with the continuous development of crop bioengineering and molecular agriculture, creating a generation of transgenic crops and genetically modified organisms which will improve sustainable and nutritious food sources.

It is envisioned that the introduction of transgenic crops will result in healthier food which will improve both macronutrient and micronutrient content and also its diesase-limiting potential. Transgenic plants as vectors for active and passive oral immunizations will be of great benefit to children and other sectors of the population at risk.

Molecular medicine, on the other hand, is focused on human growth, development and behavior, and continues to define and identify pathophysiologies, including inborn errors of metabolism, congenital malformations, degenerative diseases, obesity, and cancers. Markers of potential disease will provide early warning signals leading to modification of life styles to avoid or minimize a disease. Molecular biology and biotechnology have facilitated the production of vaccines and pharmaceuticals and diagnostic kits.

We have gone through the industrial revolution and the information technology or computer-based revolution. The next great revolution will be the genomics revolution. And it is now upon us.

It is the world's good fortune that the dizzying potentials of molecular medicine and agriculture are promising. A word of caution: the molecular sciences can present terrifying possibilities like a two-edged sword. Hence, ethical and moral problems should be dealt with firmly.

More and more, the role of other disciplines, aside from medicine and pediatrics, has been realized to be of paramount importance in the control, prevention and management of disease. It is because of this that the development and promotion of health social sciences is now being given emphasis. Transdisciplinary approaches are recognized as neessary to look at a problem in its total context, utilizing the problem as the starting point to achieve an integrated and dynamic perspective of childhood health problems.

Aside from advocacy, community mobilization, and legislation, education (including behavior modification) are essential in the promotion of wellness and quality of life and in the prevention and management of disease.

Sustaining the Environment

As Dr. Albert Schweitzer has stated:

"Man has lost the capacity to
foresee and to
forestall
He will end by destroying the earth."

Such a gloomy prediction! But actually what we have now is what a past Director-General of the World Health Organization aptly labels as a "*Wounded Planet.*" Rising levels of pollution and environmental degradation have been associated with infections, congenital malformations, cancers, respiratory ailments, gastrointestinal infections, injuries and poisonings.

Some of these environmental problems are air and water pollution, poor food quality, toxic chemicals such as pesticides, herbicides and fertilizers, radiation and even excessive levels of noise.

Efforts to minimize or remove these environmental threats must be part of a strong advocacy program.

The "Asianization" of Civilization

Another hope, particularly for this part of the world, comes from futurist John Naisbitt and the tandem of Sid Murray-Clark and Peter Lorie who have dwelt on the Asianization of civilization. Looking into the future would mean to consider as a critical factor the "coming out" of Eastern civilization as a distinct and parallel sociopolitical, cultural and economic entity, competing, if not dominating that of the West.

Their assumptions were based on several proactive politico-economic paradigms which Asian governments have implemented. The megatrends in Asia, which according to Naisbitt, are currently changing the world are:

The transformation of nation-states ⟶ regional and global networks

The migration of people from villages to super cities

The shifting from Western influence ⟶ Asian way or

from West ⟶ East

The change from export led ⟶ consumer driven economies

From government-controlled ⟶ market driven

From labor intesive ⟶ high technology

from male dominance ⟶ empowerment of women

The Pediatrician for the Third Millenium

In the 1980's a number of papers stressed the need for pediatricians to be prepared for what has been termed as the New Morbidities, which have now become accentuated and perpetuated, intensified and multiplied by the strong winds of global change. The dream of a better world for our children undeniably is a common aspiration from the beginning of time. Working for this vision and its transformation into reality have been mankind's persistent obsession. But beyond this, we should aim for healthier, brighter, more socially adjusted and psychologically stable children.

It is true that there are remarkable improvements in the indicators of better childhood. However, there is still much to be done, and there are new challenges to address.

The challenges have been presented. Hopefully, the solutions will be provided as we move on to the next days of the Congress. Wisely, the organizers of the Congress have included topics on cildren's rights, drug abuse, tobacco and alcohol use, violence, and immunizations, among others.

Clearly, a new breed of pediatrician is needed. Pediatricians who possess new skills, a new appreciation of their roles and an understanding of how various forces are interconnected as they impact on the physical, mental, social and moral well being of our children. The pediatrician must not only be prepared but must resolve with a firm commitment and common purpose to face the transition affecting children that will inexorably come.

The pediatrician of the 21st century must prepare himself to cope with entirely different and varied problems which are not entirely biological in nature. Definitely, he has to extend himself beyond the medical aspects of child health care into his social environment.

Pediatricians have the most access to parents among health care providers. How much of our time as physicians do we give to counseling parents to prevent accidents and injuries, as a specific point for reflection? Several studies reveal that physicians believe that talking to parents about injury is important, yet they also reported not having enough time, not thinking to ask, and having more important things to do. Perhaps we need to reflect on our roles and on our own values.

A Social Contract with Our Children

Given the above scenario, the challenge, therefore, is what we as pediatricians can be to our children in the next millennium.

While the responsibility for better childhood should involve every man, woman and child themselves, pediatricians, because of their training, commitment and status in the community, are expected to assume leadership roles for better child health. Not only are they looked up to for policy and decision making, but they are requested to take lead roles in implementation of programs.

It is with some degree of proper pride that of the clinical specialties, pediatrics presents an initiative toward a halistic approach for the care of its client, the child. Emphasized in this holistic perspective is the inseparability of science and art, and the unification of knowledge in health and disease.

The pediatrician is threfore expected to be the first to draw a social contract with our children to provide them a better life and to guide their destiny and that of the whole community, the country, the world.

This, we beg of the pediatrician and other child care workers, for as Henry Wadsworth Longfellow refers to children:

"Ye are better than all the ballads
That ever were sung or said;
For ye are living poems..."

We need to change in favor of our children. the coming millennium demands no less.

BIBLIOGRAPHY

Aburdene P, et al. 1990. Megatrends 2000: Ten New Directions for the 1990's.

Barkin, S, Ryan G, Gelberg L. What pediatricians can do to further youth violence prevention - a qualitative study. Injury Prevention. 1999; 5: 53-58.

Basu A. Household influences on child mortality: evidence from historical and recent mortality trends. Soc Biol 1987; 34: 187-205

Bobadilla J, Cowley P. Designing and implementing packages of essential health services. J Intl Dev 1995; 7: 543-554.

Convention on the Rights of the Child. Adopted by the General Assembly of the nited Nations on 20 November 1989.

Drucker P. Managing for the Future: The 1990's and Beyond. New York: Truman TAlley Books/PLUME; 1992.

Frenk J, et al. Health transition in middle-income countries: new challenges for health care. Health Policy and Planning 1989; 4: 29-39.

The 10/90 Report on Health Research 1999 (Global Forum for Health Research).

Ham C. Priorty setting in health care: learning from international experience. Health Policy 1997; 42: 49-66.

Hurst J. The reform of health care: a comparative analysis of seven OECD countries. Paris, OECD, 1992.

International Cooperation in Health Research. COHRED Newsletter (Research in Action) Issue 15.

International Conference on Health Research. COHRED Newsletter (Research in Action) Issue 16, Jan-March 1999.

Investing in health research and development. Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options. Geneva, World Health Organization, 1996 (document WHO/TDR/Gen/96.1).

Kennedy P. Preparing for the Twenty-First Century. London: Harper Collins Publishers; 1993.

Korten D. Getting to the Twenty-First Centruy: Voluntary Action and the Global Agenda. Connecticut: Press; 1990.

Murray CJ, Lopez AD (eds). The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge, Harvard School of Public Health on behalf of the World Health Organization and The World Bank, 1996 (Global Burden of Disease and Injury Series, Vol I).

Naisbitt J. Global Paradox: The Bigger the World Economy the More Powerful its Smallest Players. New York: Williamm Morrow and Company; 1994.

Pardes H, Marton KG, Lander ES, Tolley HD, Ullian AD, Palmer H. Effects of medical research on health care and economy. Science 1999; 283: 36-37.

Caldwell P. Child survival: physical vulnerability and resilience in adversity in the European past and the contemporary Third World. Soc Sci Med 1996; 43: 609-619.

Razelle PE. An interpretation of the modern rise of populations in Europe-a critique. Population Studies 1994; 28.

Tanz RR. The trouble with pediatricians. Inj Prev 1999; 5: 8-10.

The World Health Report 1996-Fighting disease, fostering development. Geneva, World Health Organization, 1996.

The World Health Report 1998-Life in the 21st century: a vision for all Geneva, World Health Organization, 1998.

The World Health Report 1999-Basic indicators for all members states. Geneva, World Health Organization, 1999.

Toffler A. Powershift: Knowledge, Wealth, and Violence at the Edge of the 21st Century. New York: Bantam Books; 1991.

UNICEF (United Nations Children's Fund). 1999. The State of the World's Children 1999. New York: Oxford University Press.

World Declaration and Plan of Action from the World Summit for Children. New York. 30 September 1990.

WHO global database on child growth and malnutrition. Geneva, World, Health Organization, 1997 (document WHO/NUT/97.4).

Serum levels of eosinophilic cationic protein (ECP), myeloperoxidase (MPO), Lipid peroxidation products, interleukin (IL)-5 and interferon (IFN) – γ in children with bronchial asthma at acute asthma attack and remission*

Ömer Kalaycı[1], Yıldız Saraçlar[1], Kamer Kılınç[2], Bülent E. Şekerel[1]

Hacettepe University Faculty of Medicine [1]Department of Pediatrics, [2]Department of Biochemistry, Ankara, Turkey

SUMMARY: Kalaycı Ö, Saraçlar Y, Kılınç K, Şekerel BE. Serum levels of eisonophilic cationic protein (ECP), myeloperoxidase (MPO), lipid peroxidation products, interleukin (IL)-5 and interferon (IFN)-γ in children with bronchial asthma at acute asthma attack and remission. Turk J Pediatr 2000; 42: 9-16.

We determined serum levels of myeloperoxidase (MPO), eosinophilic cationic protein (ECP), reactive oxygen species measured as thiobarbituric acid reactive substances (TBARS), interleukin (IL)-5, and interferon (IFN)-γ in 14 asthmatic children during an asthma attack and remission. Twelve healthy children served as controls. In atopic asthmatics, asthma attack resulted insignificant elevations of ECP, MPO, and TBARS compared to remission. TBARS levels were also higher at remission compared to controls. However, there was a great deal of overlap in the values of asthmatics and controls. IL-5 and IFN-γ were detectable at low levels and only in a few patients. These results provide further evidence for participation of eosinophils, neutrophils and reactive oxygen species in the pathogenesis of acute asthma, and suggest that their products may be used in monitoring asthma attack. Serum IL-5 and IFN-γ levels are not appropriate for use in the follow-up of asthmatic children.

Key words: eosinophilic protein, interleukin (IL)-5, interferon (IFN)-γ, lipid peroxide, myeloperoxidase.

Recent studies have shown that airway inflammation is a persistent feature of asthma even in its mildest forms and during asymptomatic periods[1]. A subgroup of T lymphocytes (Th-2) that synthesize mainly interleukin (IL)-4 and IL-5 and little interferon (IFN)-γ and eosinophils have a key role in the inflammation of allergic asthma[2-4]. Although the role of neutrophils is not as clear, there is some data to indicate that neutrophils are important in the late asthmatic response[5]. Production of reactive oxygen species (ROS), a major mechanism by which both neutrophils and eosinophils participate in human defense, has also been implicated in the pathogenesis of bronchial asthma[6].

Although inflammation is the underlying factor, markers of inflammation to aid in diagnosis and follow-up of asthma have not entered into clinical use; currently, clinical findings and pulmonary function tests are the only tools that serve this purpose. This presents some difficulties, especially for childhood asthma, as symptoms of the disease can be quite nonspecific and pulmonary function tests are not reliable in children younger than five years of age. Furthermore, there can be a great deal of discrepancy between pulmonary function tests and symptoms, even in adults[7]. Clearly, easily measurable objective markers to aid in the diagnosis and follow-up of asthma would be quite useful. Among these markers are serum levels of eosinophilic cationic protein (ECP), IL-5[8], myeloperoxidase (MPO)[9], and lipid peroxidation products (as an indirect measure of ROS)[10,11]. ECP, as a marker of eosinophil

* This work was supported by a grant from Hacettepe University Research Support Foundation (grant # 96.01.101.010).

activity, has been the subject of intense investigation, and it is generally believed to be a good marker of disease activity[8,12,13]. Unlike with eosinophils, the data about neutrophils is scarce and controversial[14-17]. MPO is believed to reflect neutrophil activity, as 95 percent of the protein is derived from these cells, whereas the remaining five percent is contributed by monocytes. Therefore, MPO is believed to be an appropriate marker for neutrophil activation.

In vitro studies have clearly defined the significance of ROS in bronchial asthma[6,18-20]. However, since ROS are very quickly removed or scavenged by local mechanisms, it is very difficult to measure them directly in biologic systems. ROS can act on membrane phospolipids and cause lipid peroxidation. Measurement of thiobarbituric acid reactive substances (TBARS) is a good marker for ROS production[21], There are conflicting reports about the serum levels of lipid peroxides and their significance in bronchial asthma[10,11,22].

The aim of this study was to measure the serum levels of ECP, MPO, TBARS, IL-5, and IFN-γ in a group of asthmatic children. Levels were determined during a period of hypoxia (acute asthma attack) and 30 days after discontinuation of all medical treatment (remission). Patients with possible confounding factors like medication usage or presence of infections were excluded from the study. We also investigated whether these indices had any relation to the level of hypoxia and pulmonary function parameters.

Material and Methods

Patients

Fourteen children, aged 3-15 years, who presented with an acute asthma attack to the emergency department of Hacettepe University, İhsan Doğramacı Children's Hospital were included in this study. The patients had to fulfill the following criteria in order to be eligible for the study:

1. Moderate to severe asthma attack[23].
2. Hypoxia: oxygen saturation < 95 percent.
3. Improvement (15%) in FEV1 after salbutamol inhalation during the asthma attack or following recovery.
4. No bronchodilator or antiinflammatory treatment before or during presentation to the hospital and no history of immunotherapy.
5. No current infection or systemic disease except bronchial asthma.

Control Group

Twelve healthy age-matched children without any systemic or atopic diseases served as the control group. In order to ensure the control group had no atopy, their sera were tested for the presence of specific IgE for a combination of antigens (All Screen Inhalation, Melja Diagnostik, Kassel, Germany): Dermatophagoides pteronyssinus, cat, dog, phleum pratense, secale cereale, cladosporium, artemisia vulgaris, and betula verrucosa. To be included in the study the children had to have a negative result on this test. The sera of the control group, like that of the study population, were tested for ECP, MPO, IL-5, IFN-γ and TBARS. Only eight samples could be tested for ECP, where as all 12 samples were tested for the other parameters.

Design

Blood (15-20 ml) was drawn from the radial artery of each patient upon presentation with an acute asthma attack. From this sample, blood-gas determination, complete blood count and differential, and total eosinophil count[24] were done, and serum was separated and stored at -20 °C until analysis for measurement of total and specific IgE, ECP, MPO, IL-5, IFN-γ and TBARS. Pulmonary functions were also measured (2130 PFT system, Sensor Medics, CA, USA). All patients were then treated according to a standard protocol involving nebulized salbutamol and oral prednisolone. Patients were followed in the emergency room until their oxygen saturation was > 95 percent at room air or their FEV1 was > 75 percent of the predicted. After discharge from the emergency room, oral methylprednisolone was tapered to zero in 7-10 days. During this period all patients used inhaled salbutamol via a spacer starting with 200 μg every two hours and then at longer intervals. Upon recovery, both corticosteroid and salbutamol were discontinued and patients were called for a follow-up visit in 30 days, when pulmonary functions and blood tests were repeated. One day later, all patients were skin tested with common aeroallergens and food allergens.

Assessment of Atopy

Patients were skin-prick tested with a battery of antigens including house dust mite species,

animal antigens, American cockroach, grass weed and tree pollens, milk and egg white. An induration 3 mm greater than the negative control associated with surrounding erythema was considered positive[25]. If the results of skin-prick testing were negative, intradermal tests were done with the same antigens. Each patient's serum was then tested for the presence of specific IgE with the relevant antigen(s) (AlaSTAT, Diagnostic Products Corporation, Los Angeles, CA, USA). To be considered atopic, patients had to have at least one positive skin prick and a greater than class 2 specific IgE with the antigen(s). Nonatopic patients had negative skin-prick and intradermal tests and a less than class 1 specific IgE to aeroallergens.

Blood Collection and Handling

Blood samples were drawn from the radial artery in the study group and from the antecubital vein in the control group and were transferred to a serum separating tube (Becton Dickinson, Mountain View, CA, USA) and allowed to clot at room temperature for 60 minutes (min). Samples were then centrifuged at 1350 g for 10 min. The serum was separated, aliquoted and stored at -20 °C until analysis.

Eosinophilic cationic protein (ECP) and MPO were measured by radioimunosorbent assay (RIA) using Pharmacia kits (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden), and IL-5 and IFN-γ by enzyme linked immunosorbent assay (ELISA) using cytoscreen immunoassay (Biosource International, CA, USA). The lowest detection limit was < 4 pg/ml for both IL-5 and IFN-γ.

Serum lipid peroxide levels were determined measuring thiobarbituric acid (TBA) reactivity as described by Wade and van Rij[26]. Briefly, 200 µl of trichloroacetic acid (TCA) (25 g TCA in 10 ml distilled water) was added to 1 ml of serum. The mixture was centrifuged at 1000 g for 10 min, and the precipitate was reacted with 1 ml of 0.67% TBA (w/v). The samples were heated at 100 °C for 30 min. After centrifugation, the absorption of malondialdehyde (MDA)-TBA chromogen was measured at 532 nm. Tetramethoxy propane was used as malondialdehyde standard. TBA reactivity was calculated as micromole MDA per liter (µM).

Statistical Analysis

All statistical analyses were done using SPSS 6.0 statistical program. For comparisons between the acute attack and remission periods of asthma patients, Wilcoxon paired samples test was used, and Mann Whitney U test was used for comparison of asthma patients with controls. Correlations between parameters were studied using Pearson's test. Values are expressed as mean ± standard error of the mean (SEM). A significance level of five percent was used unless stated otherwise.

Results

Fourteen patients that presented with moderate to severe asthma attack to the emergency room of İhsan Doğramacı Hospital were included in the study. Of the 14 patients, 11 were atopic and three nonatopic. Nonatopic patients' asthma attacks were due to exposure to cigarette smoke in two and to automobile exhaust in one patient. Characteristics of the patients are summarized in Table I. Mean ages of the atopic patients and controls were 9.3 ± 1.2 and 10.1 ± 1.0 years, respectively ($p > 0.05$). The results of the three nonatopic patients are summarized in Table II and those of atopic asthmatics and controls are given below.

Table I. Characteristics of Asthma Patients

Patient no.	Age (years), gender	Specific IgE class*			Total IgE (IU/ml)
		Grass	Weed	Dust mite	
1	8,F	3			1988
2	5,M			4	533
3	9.5,F	3	4	4	1022
4	10,M		2		48
5	14,M	1		4	507
6	8,M	4	3	3	813
7	13,M	1		2	171
8	3,F			2	82
9	13,M	4	2		1450
10	15,M	4		3	2276
11	4,M	4			35
12#	12,M	–	–	–	13
13#	7,M	–	–	–	44
14#	5,M	–	–	–	63

*: Patients 1, 3, 4, 6 and 7 also had positive skin prick tests with trees and patient 11 with cat, but specific IgE results for these antigens were not available.

#: Nonatopic patients.

Table II. Results of the Nonatopic Asthmatic Children (Asthma Attack/Remission)

Patient no.	Leukocyte count (mm^3)	Eosinophil count (mm^3)	FEV1 (% predicted)	PaO_2 mmHg	ECP µg/L	MPO mg/L	TBARS µM
12	5200/5600	105/120	69/79	73/86	8/4	406/250	5.41/3.67
13	17500/7900	200/300	38/110	71/138	16/40	482/615	4.28/3.79
14	7500/7500	225/300	59/102	75/96	7/14	303/485	3.28/3.00

ELP: eosinophilic cationic protein; MPO: myeloperoxidase; TBARS: thiobarbituric acid reactive substances.

Leukocyte and Eosinophil Counts: The mean leukocyte count was 9,845 ± 1,161 and 7,154 ± 517/mm^3 at asthma at asthma attack and remission, respectively ($p > 0.05$). Similarly, the eosinophil count did not differ at asthma attack (336 ± 120 mm^3) and remission (290 ± 58 mm^3) ($p > 0.05$). Evaluation of the differential counts failed to show any difference in the numbers of neutrophils, lymphocytes, or monocytes between these two periods (data not shown).

FEV1 and PaO_2: Pulmonary functions were measured in eight patients. The mean of FEV1 as percentage predicted was 52.5 ± 5.2 at asthma attack and 94.3 ± 4.8 at remission (Fig. 1a); the difference was significant ($p = 0.01$). The mean of PaO_2 was also significantly lower at asthma attack (68.9 ± 1.8 mmHg) compared to remission (102.0 ± 4.0 mmHg) ($p = 0.003$) (Fig. 1b).

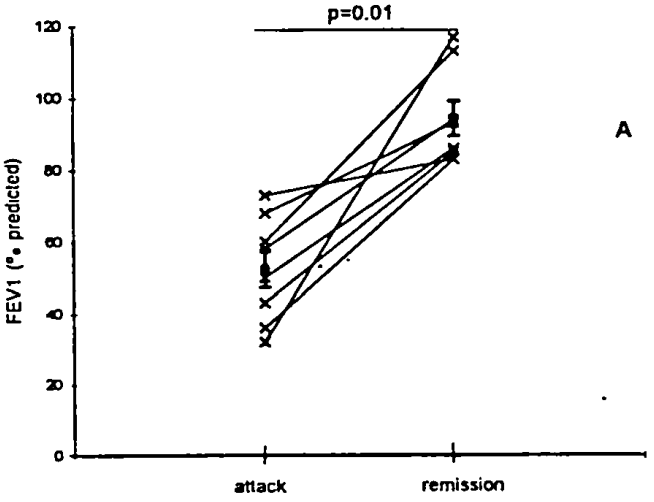


Fig. 1. FEV1 (A) and PaO_2.

ECP: The mean of ECP at asthma attack (50.1 ± 17.1 µg/L) was significantly higher than at remission (12.4 ± 2.1 µg/L) ($p = 0.003$). However, the mean ECP of controls (8 patients) (19.5 ± 2.8) was not statistically different from the value obtained at remisision (Fig. 2a).

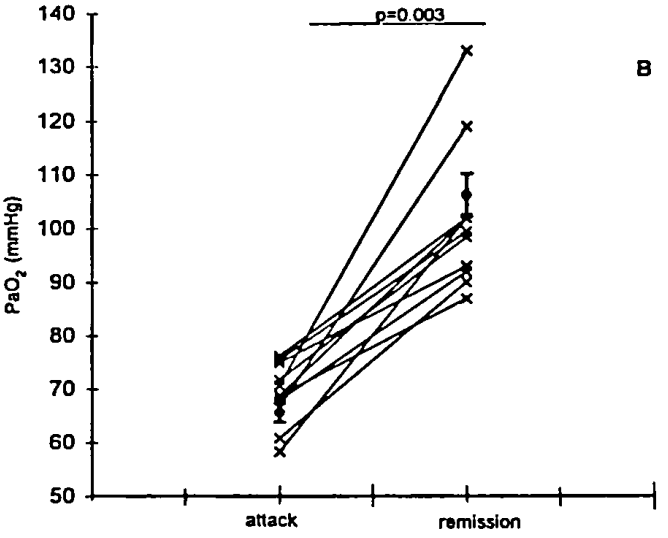


Fig. 1. FEV1 (B) and values and their means in individual atopic patients.

MPO: The results obtained for MPO were similar to those for ECP. Although a difference was observed between asthma attack (664.3 ± 118.4 µg/L) and remission (323.2 ± 40.4 µg/L) ($p = 0.004$), values of the control group (399.3 ± 48.6 µg/L) were not statistically different from the values obtained at remission (Fig. 2b).

TBARS: Atopic asthmatics had a significantly higher serum TBARS at asthma attack (4.1 ± 0.2 µM) compared to remission (2.8 ± 0.2 µM) ($p = 0.003$) (Fig. 2c). The mean of controls was 2.2 ± 0.2. The difference between the remission period and the controls just failed to reach statistical significance ($p = 0.06$). In fact, when atopic and nonatopic asthmatics were pooled, this difference actually reached statistical significance ($p = 0.018$) (Fig. 2d). However, there was a notable overlap in these values.

IL-5 and IFN-γ: Both cytokines were undetectable in the majority of samples. In the few samples where levels were within detection limits, their concentrations were quite low and close to the lower limit of detection.

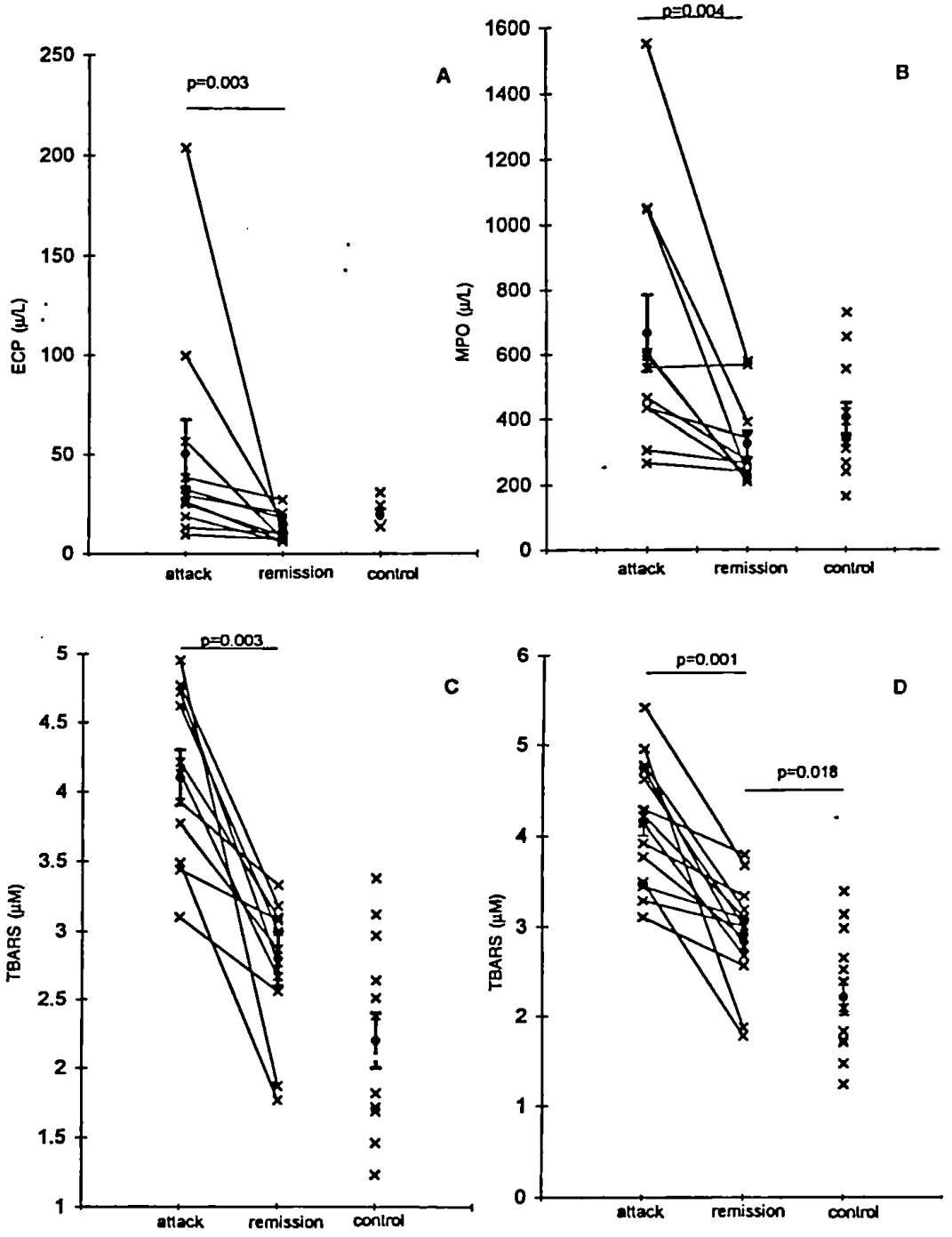


Fig. 2. ECP (A), MPO (B), and TBARS (C) values and their means in atopic patients at asthma attack and remission. 2D depicts the TBARS levels of all asthmatic children, including both atopic and nonatopic patients.

Correlation Analyses

As expected, FEV1 and PaO_2 showed a very high correlation in atopic patients ($r = 0.88$, $p < 0.001$). Similarly, ECP and eosinophil counts also showed a significant correlation in this group ($r = 0.69$, $p < 0.001$). However, ECP failed to show a significant correlation with either FEV1 and PaO_2 ($p > 0.05$ for both). MPO, on the other hand, while showing a significant correlation with PaO_2 ($r = -0.57$, $p = 0.006$) (Fig. 3a), did not disclose any correlations with other parameters studied, including leukocyte count.

Thiobarbituric acid reactive substances (TBARS) showed a high and significant correlation both with PaO_2 ($r = -0.56$, $p = 0.002$) (Fig. 3b), and with FEV1 ($r = -0.57$, $p = 0.0069$ (Fig. 3c).

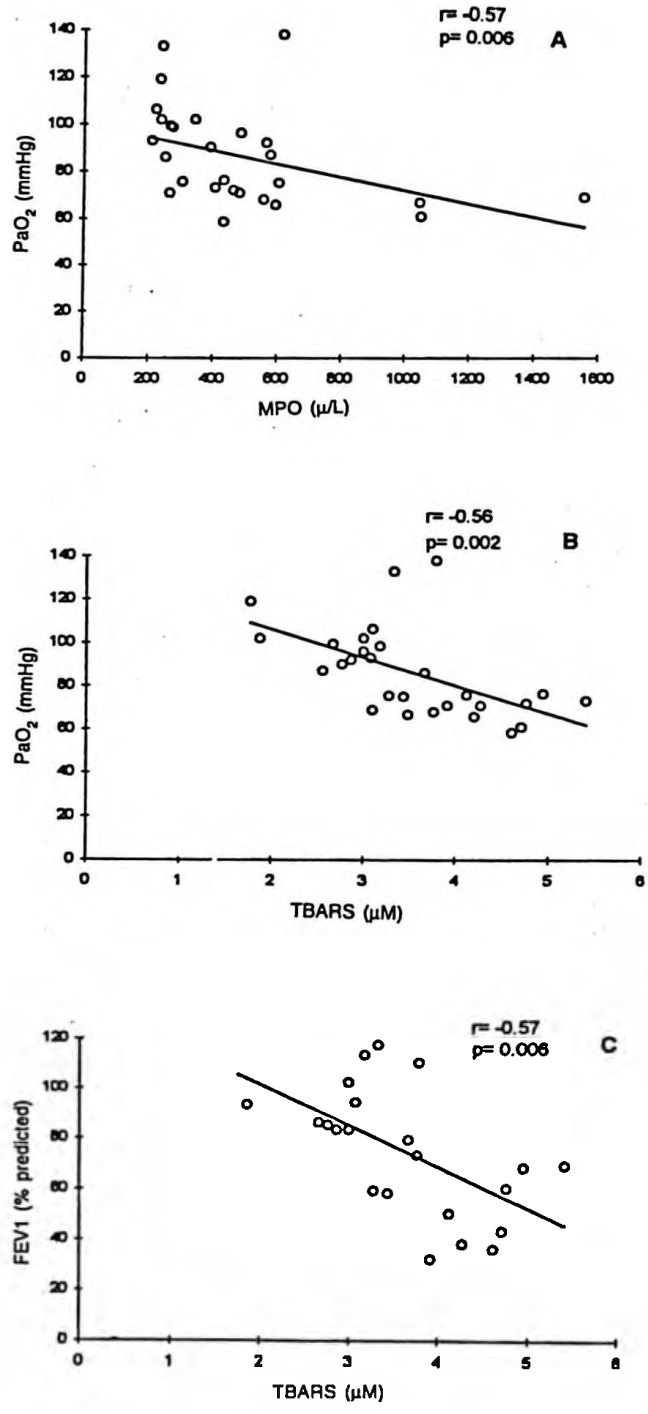


Fig. 3. Correlations between MPO-PaO_2 in atopic asthmatics (A), and TBARS-PaO_2 (B) and TBARS-FEV1 (C) in all asthmatic children, including both atopic and nonatopic patients.

Discussion

The results of our study confirm the participation of eosinophils, neutrophils, and reactive oxygen species in acute asthma, and further suggest that their products may be used as objective markers in the follow-up of acute asthma attack. However, the significant overlap observed in controls and asthmatics in all three variables indicates that they are not useful to differentiate asthmatics from normal controls. Furthermore, due to the design of our study, we cannot draw conclusions regarding the utility of these markers in the long term follow-up of chronic asthma. The other markers investigated in this study, measurement of serum IL-5 and IFN-γ levels, failed to produce any consistent results. In fact, they were undetectable in most of the samples. However, it should be pointed out that our findings do not contradict the importance of local production of

these cytokines. It is well documented that eosinophils are key effector cells in atopic asthma. Although total eosinophil count has been suggested to indicate the ongoing inflammation in asthma, it is claimed that eosinophilic proteins better reflect eosinophilic activity[13,27,28]. Our findings are also in favor of this hypothesis. It is difficult to reach conclusions regarding ECP in nonatopic patients because of their limited number. However, in two nonatopic patients, serum ECP level was actually higher in remission that it was in acute attack, a trend that was not observed in any of the atopic patients This finding implies that serum ECP may not provide valuable information in nonatopic patients. The reports about ECP in the medical literature are conflicting[29-32]. As suggested by Motojima et al.[8], these results may stem from the differences in the patients, in the severity of asthma, in medication usage and in serum separation techniques.

Myeloperoxidase (MPO) levels obtained at the time of an asthma attack, at remission and in controls followed a similar trend to those of ECP. In addition, MPO correlated significantly with PaO_2, suggesting that hypoxia contributed significantly to the increases in MPO and supporting our previous observations in rats[33]. Similar to ECP, MPO levels also decreased in 10 of 11 atopic patients after the asthma attack. In one patient only the level remained stable. This consistent trend was not observed in nonatopic asthmatics. In two nonatopic patients the levels of MPO at acute asthma attack were actually lower than they were at remission. Taken together, these findings suggest that a combination of the atopic state and hypoxia may have contributed to the activation of leukocytes resulting in increased MPO. This study, like many others, supports the notion that neutrophils play a significant role in asthma. In the study by Scher et al.[9], for instance, MPO was found to increase in asthmatic patients. Similar to our study, this increase did not correlate consistently with increases observed in eosinophilic proteins, nor with pulmonary function tests.

Thiobarbituric acid reactive substances (TBARS) differend from ECP and MPO in that asthmatics had significantly higher values even at remission compared to controls. Still, it is difficult to claim that this finding reflects an ongoing oxidant stress even during asymptomatic periods in asthma because there was a remarkable overlap in the values obtained in asthmatics and controls. Most of the studies that have investigated the role of ROS in asthma are conducted in in vitro and ex vivo systems[34-36]. The studies that have looked into this question by determining lipid peroxidation products are limited and have produced conflicting results[10,11,22]. Owen et al.[10] showed that a lipid peroxidation product, phospholipid esterified 9, 11 linoleic acid (PL-9, 11-LA), is increased in serum in asthmatic patients compared to controls. They have further found that this increase is more pronounced in acute compared to chronic asthma. These findings are in accordance with our study. In another study, however, totally different results were obtained[22]. In this study PL-9, 11-LA was serially measured in eight patients and failed to show any increase at any time point starting from an acute asthma attack. Five of these patients were using antiinflammatory treatment while the remaining three were on bronchodilators. Many drugs, including teophyllin, are known to effect lipid peroxide levels[37,38]. The results of this study may have been confounded by the concomitant medication usage. Another major difference between our and the two above referenced studies[10,22] is that both of the latter were conducted in adult populations which may, in part, be responsible for the different results.

Further studies using larger sample sizes and also serial measurements are needed to define the precise value of these parameters in the follow-up of asthma.

REFERENCES

1. Kay AB. Asthma and inflammation. J Allergy Clin Immunol 1997; 87: 893-890.
2. Wardlaw AJ, Dunette S, Gleich GJ, et al. Eosinophils and mast cells in bronchoalveolar lavage in mild asthma: relationship to bronchial hyperreactivity. Am Rev Respir Dis 1988; 137: 62-69.
3. Parronchi P, Macchia D, Piccinni MP, et al. Allergen and bacterial antigen-specific T cell clones established from atopic donors show a different profile cytokine production. Proc Natl Acad Sci USA 1991; 88: 4538-4542.
4. Robinson DR, Hamid Q, Ying S, et al. Evidence for a predominant Th-2 type bronchoalveolar lavage T lymphocyte population in atopic asthma. N Engl J Med 1992; 326: 298-304.
5. Metzger WJ, Richerson HB, Worden K, et al. Bronchoalveolar lavage of allergic asthmatic patients following allergen provocation. Chest 1986; 86: 477-483.

6. Calhoun WJ, Bush RK. Enhanced reactive oxygen species metabolism of airspace cells and airway inflammation follow antigen challenge in human asthma. J Allergy and Clin Immunol 1990; 86: 306-313.
7. Kendrick AH, Whitfield MJ, Laszlo G. Accuracy of perception severity of asthma: patients treated in general practice. Br Med J 1993; 307: 422-424.
8. Motojima S, Akutsu I, Fukuda T, et al. Clinical significance of measuring levels of sputum and serum ECP and serum IL-5 in bronchial asthma. Allergy 1993; 48: 98-106.
9. Scher A, Berman D, Weinberg EG, et al. Granulocyte proteins in serum in childhood asthma: relation to spirometry and therapy. Clin Exp Allergy 1996; 26: 1131-1141.
10. Owen S, Pearson D, Suarez Mendez V, et al. Evidence of free radical activity in asthma. N Engl J Med 1991; 325: 586-587.
11. Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COPD, and smokers. Am J Respir Crit Care Med 1996; 154: 1055-1060.
12. Carlson M, Hakansson L, Petersen C, et al. Secretion of granule proteins from eosinophils and neutrophils is increased in asthma. J Allergy Clin Immunol 1991; 87: 27-33.
13. Venge P, Dahl R. Are blood eosinophil number and activity important for the development of the late asthmatic reaction after allergen challenge? Eur Respir J 1989; 2 (Suppl): 430-434.
14. Murphy KR, Wilson MC, Irvin CG, et al. The requirements for polymorphonuclear leukocytes in the late asthmatic response and heightened airways reactivity in animal model. Am Rev Respir Dis 1986; 134: 62-68.
15. Hutson PA, Varley JG, Sanjar S, et al. Evidence that neutrophils do not participate in the late phase airway response provoked by ovalbumin inhalation in conscious, sensitized guinea pigs. Am Rev Respir Dis 1990; 141: 535-539.
16. Frangova V, Sacco O, Silvestri M, et al. BAL neutrophilia in asthmatic patients. A by-product of eosinophil recruitment? Chest 1996; 110: 1236-1242.
17. Teran LM, Carroll MP, Frew AJ, et al. Leukocyte recruitment after local endobronchial allergen challenge in asthma. Relationship to procedure and to airway interleukin-8 release. Am J Respir Crit Care Med 1996; 154: 469-476.
18. Renkema TE, Postma DS, Noordhoek JA, et al. Association between bronchial hyperreactivity and superoxide anion production by polymorphonuclear leukocytes in chronic airway obstruction. Agents Actions 1989; 26: 52-54.
19. Masahiko K, Nakano M, Morikawa A, et al. Ability of polymorphonuclear leukocytes to generate active oxygen species in children with bronchial asthma. Int Arch Allergy Appl Immunol 1991; 95: 17-22.
20. Janjoun NN, Calhoun WJ. Enhanced production of oxygen radicals in asthma. J Lab Clin Med, 1994; 123: 131-137.
21. Dormady TL. An approach to free radicals. Lancet 1983; 2: 1010-.
22. Chilvers ER, Garratt H, Whyte MK, et al. Absence of circulating products of oxygen derived free radicals in acute severe asthma. Eur Respir J 1989; 2: 950-954.
23. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. National Heart Lung and Blood Institute/World Health Organization Workshop Report. National Institutes of Health Publication number: 95-3659. January 1995.
24. Dacie JV, Lewis SM. Practical Hematology (3rd ed). New York: Grune and Stratton Inc; 963: 19.
25. Dreborg S (ed). Skin tests used in type I allergy testing. Allergy 1989: 44 (Suppl); 1-594.
26. Wade Cr, van Rij AM. Plasma thiobarbituric acid reativity: reaction conditions and the role of iron, antioxidants and lipid peroxy radicals on the quantitation of plasma lipid peroxides. Life Sci 1988; 43: 1085-1093.
27. Kay AB. Eosinophils as effector cells in imunity and hypersensitivity disoders. Clin Exp Immunol 1985; 62: 1-12.
28. Zimmermann B, Lanner A, Enander I, et al. Total blood eosinophils, serum eosinophil cationic protein and eosinophil protein X in childhood asthma: relation to disease status and therapy. Clin Exp Allergy 1993; 23: 564-570.
29. Griffin E, Hakansson L, Formgren H, et al. Blood eosinophil number and activity in relation to lung function in patients with asthma and with eosinophilia. J Allergy Clin Immunol 1991; 87: 548-557.
30. Vatrella A, Ponticiello A, Parrella R, et al. Serum ECP as a marker of disease activity and treatment efficacy in seasonal asthma. Allergy 1996; 51: 547-555.
31. Backman KJ, Jarvinen P, Sorva R. Serum eosinophilic cationic protein during treatment of asthma in children. J Allergy Clin Immunol 1993; 92: 34-38.
32. Durham SR, Loegering DA, Dunnette S, et al. Blood eosinophils and eosinophil derived proteins in asthma. J Allergy Clinn Immunol, 1989; 84: 931-936.
33. Inan C, Kilic I, Kilinc K, et al. The effect of high dose antenatal vitamin E on hypoxia induced changes in newborn rats. Pediatr Res 1995; 38: 1-5.
34. Lansing MW, Mansour E, Ahmet A, et al. Lipid mediators contribute to oxygen radical induced airway responsiveness in sheep. Am Rev Respir Dis 1991; 144: 1291-1296.
35. Lansing MW, Ahmet A, Cortes A, et al. Oxygen radicals contribute to antigen induced airway responsiveness in conscious sheep. Am Rev Respir Dis 1993; 147: 321-326.
36. Postma DS, Renkema TEJ, Noordhoek JA, et al. Association between nonspecific bronchial hyperreactivity and superoxide anion production by polymorphonuclear leukocytes in chronic air-flow obstruction. Am Rev Respir Dis 1988; 137; 57-61.
37. Struhar D, Kivity S, Topilsky M. Quinacrine inhibits oxygen radicals release from human alveolar macrophages. Int J Immunopharmac 1992; 14: 275-277.
38. Godard P, Chaintreuil J, Bensadoun J, et al. Long term treatment with theophylline increases malonyl dialdehyde plasma concentrations. Thorax 1984; 39: 137-139.
39. Corrigan CJ, Haczku A, Gemou-Engesaetg V, et al. CD4 T lymphocyte activation in asthma is accompanied by increased serum concentrations of IL-5. Effect of glucocorticoid therapy. Am Rev Respir Dis 1993; 147: 540-547.

Serum levels of antioxidant vitamins (alpha tocopherol, beta carotene, and ascorbic acid) in children with bronchial asthma

Ömer Kalaycı[1], Tanju Besler[2], Kamer Kılınç[3], Bülent E. Şekerel[1], Yıldız Saraçlar[1]

[1]Department of Pediatrics, Hacettepe University Faculty of Medicine, [2]Department of Dietetics Hacettepe University School of Health Technology, and [3]Department of Biochemistry Hacettepe University Faculty of Medicine, Ankara, Turkey.

SUMMARY: Kalaycı Ö, Besler T, Kılınç K, Şekerel BE, Saraçlar Y. Serum levels of antioxidant vitamins (alpha tocopherol, beta carotene, and ascorbic acid) in children with bronchial asthma. Turk J Pediatr 2000; 42: 17-21.

We determined serum levels of alpha tocopherol, beta carotene, and ascorbic acid and lipid peroxidation products (thiobarbituric acid reactive substances-TBARS) in 14 children during an asthma attack and remission. Twelve healthy children served as controls. All antioxidant vitamins were significantly lower in asthmatics at remission compared to controls. Comparison of attack and remission periods in asthmatic patients failed to reveal any difference except in beta carotene ($p = 0.03$). The levels of all three vitamins correlated very significantly with each other ($r = 0.89$-0.95). TBARS levels were significantly higher at asthma attack compared to remission ($p = 0.001$). No correlation was observed between the antioxidant vitamins and lipid peroxidation products. This study shows that antioxidant vitamins are decreased in sera of asthmatic patients even during the asymptomatic periods of the disease, and that this decrease is not totally dependent on the increased oxidative stress as reflected by lipid peroxidation products. The role of antioxidant vitamins in prevention and/or treatment of asthma remains to be determined.

Key words: alpha tocopherol, ascorbic acid, beta carotene, bronchial asthma, thiobarbituric acid reactive substances.

A variety of mediators are released by the inflammatory cells that reside within the lung and cause the tissue destruction and inflammation that are characteristic of asthma. Among these mediators are reactive oxygen (ROS) produced by eosinophils, neutrophils, and macrophages. The role that is played by ROS in asthma has been demonstrated by in vitro studies[1-13]. The data from in vivo systems, however, are scarce and conflicting. In the in vivo studies, as the direct measurement of ROS in biologic systems is difficult due to their high reactivity or rapid clearance measurement of lipid peroxidation products has been used as a sensitive indicator of ROS activity[14]. In this context, Owen et al.[15] and Rahman et al.[16] have shown increased lipid peroxidation in asthmatics, whereas the data obtained by Chilvers et al.[17] failed to show the presence of circulating products of ROS in asthma.

Several antioxidant defenses are normally present in pulmonary tissue including catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, vitamin C, vitamin E, and β carotene[18]. It has recently been demonstrated that in addition to enhanced lipid peroxidation, vitamin C and vitamin E are decreased in the BAL fluid of guinea pigs following an asthmatic response[18]. The data regarding the relationship between antioxidant vitamins and asthma is limited. Recently, Dow et al.[19], using a food frequency questionnaire, showed that vitamin E may influence lung function in the elderly, whereas vitamin C did not have this effect. The studies with vitamin C have in general failed to produce consistent results[20]. The aim of this study was to investigate the possible changes in antioxidant vitamin levels and their relationship to the oxidant stress produced by asthma. For this purpose, we measured the serum levels of thiobarbituric acid reactive substances (TBAR) and of antioxidant vitamins, ascorbic acid (vitamin C), α tocopherol (vitamin E) and β carotene (provitamin A) in a group of asthmatic children

and compared them to the levels obtained from healthy controls. Levels were determined during a period of hypoxia (acute asthma attack) and 30 days after discontinuation of all medical treatment.

Material and Methods

Patients and Controls

Fourteen children, aged 13-15 years, who presented with a moderate to severe acute asthma attack[21] to the emergency department of Hacettepe University, İhsan Doğramacı Children's Hospital were included in this study. The asthma attack was due to allergens in 11 and to nonspecific airway irritants in three patients. None of the children had malnutrition or growth retardation.

Twelve healthy age-matched children without any systemic or atopic diseases, who also had normal physical examination findings, served as the control group.

Design

Blood (15-20 ml) was drawn from the radial artery of each patient upon presentation with an acute asthma attack. From this sample blood-gas determination was done and serum was separated and stored at -20 °C until analysis. Pulmonary functions were also measured (2130 PFT system. Sensor Medics, CA, USA). All patients were treated according to a standard protocol with oral corticosteroids and inhaled salbutamol. Upon complete recovery from the acute excarbation, both medications were discontinued and patients were called for a follow-up visit in 30 days. At the follow-up visit, in addition to measuring pulmonary functions, all blood tests that were done at study entry were repeated. One day later, in order to determine their atopic status, all patients were skin tested with common aeroallergens and food allergens.

Serum lipid peroxide levels were determined by measuring thiobarbituric acid (TBA) reactivity as described by Wade and van Rij[22].

Determination of Vitamins

Serum Vitamin E concentration was measured using the method described by Desai[23]. The intra-and inter-assay of coefficient variation for the measurement were 2.1 and 3.4 percent, respectively. The colorimetric method was employed for asay of beta carotene[24,25]. Intra- and inter-assays of coefficient variation in beta carotene measurements were calculated as 3.8, and 1.8 percent, respectively. Analysis of vitamin C was conducted using the colorimetric method using 2,6-dichlorophenol-indophenol[26].The intra-and inter-assay variations for the vitamin C assay in the study were 2.7 and 4.4 percent, respectively.

Statistical Analysis

All statistical analyses were done using SPSS 6.0 statistical program. For comparisons between the acute attack and remission periods of asthma patients, Wilcoxon paired samples test was used, and comparison of asthma patients and controls. Mann Whitney U test was used for comparison of asthma patients and controls. Correlations between parameters were studied using Pearson's test. Values are expressed as mean ± standard error of the mean (SEM). A significance level (p value) of five percent was used unless stated otherwise.

Results

Of the 14 patients, 11 were atopic and three nonatopic. Mean ages of the patients and controls were 9.0 ± 1.0 and 10.1 ± 1.0 years, respectively ($p > 0.05$). Pulmonary functions were measured in 11 patients. The mean of FEV1 as % predicted was 53.3 ± 4.3 at asthma attack and 95.0 ± 4.1 at remission ($p < 0.001$). The mean of PaO_2 was also significantly lower at asthma attack (69.8 ± 1.5 mmHg) compared to remission (103.0 ± 4.3 mmHg) ($p < 0.001$).

Lipid Peroxides: Patients had significantly higher serum TBARS at asthma attack (415 ± 0.18 μM) compared to remission (2.90 ± 0.15 μM) ($p = 0.001$) (Fig. 1). The mean of controls was 2.2 ± 0.2. The difference between levels during the remission period and in controls was also significant ($p = 0.018$) (Fig. 1). There was a great deal of overlap in the values of these two groups.

Antioxidant Vitamins: Serum levels of ascorbic acid and alpha tocopherol did not disclose any statistical significance between asthma attack and remission (Fig. 2a, 2b). Beta carotene, however, was higher in the remission period compared to the asthma attack ($p = 0.03$) (Fig. 2c). Comparison of antioxidant vitamin levels between the remission period of asthmatic patients and in controls revealed highly

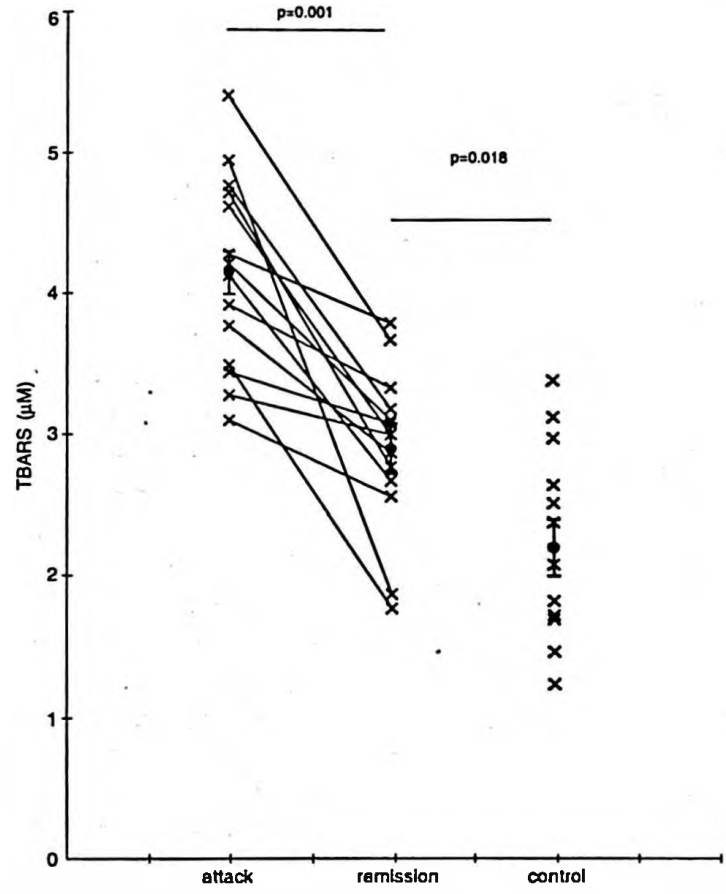


Fig. 1. Levels of thiobarbituric acid reactive substances (μM TBARS) in sera of asthma patients and controls. (-) and error bars denote mean ± SEM.

significant differences for all three vitamins studied (Fig. 2). Interestingly, in asthmatic patients the levels of ascorbic acid, β carotene, and α tocopherol correlated significantly with each other, with r values ranging between 0.89 and 0.95 (Fig. 3). No correlation was found between any of the vitamins and TBARS, PaO_2 or FEV1 ($p > 0.05$ for each).

Discussion

The results of this study confirm previous observations that there is an oxidative stress in asthma and extend further the concept that this oxidative stress is associated with significantly decreased levels of all three antioxidant vitamins, (ascorbic acid, β carotene, and α tocopherol). Although both FEV1 and PaO_2 returned to normal levels, the level of TBARS was still statistically higher compared to controls even after the acute asthma attack subsided. However, it should be noted that despite this statistical significance there is a great deal of overlap between the TBARS values obtained in the remission period with those obtained in the control group.

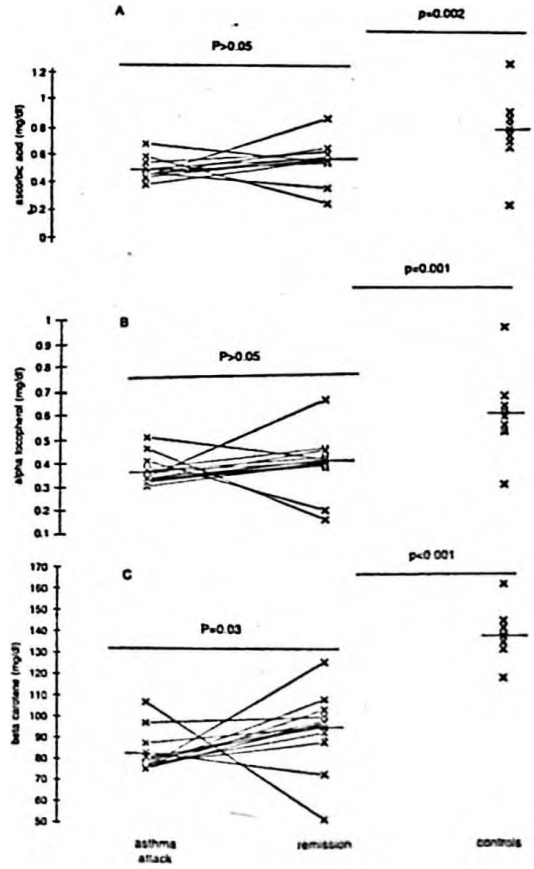


Fig. 2. Antioxidant vitamin levels in sera of asthma patients and controls: – shows the mean for each set of values.

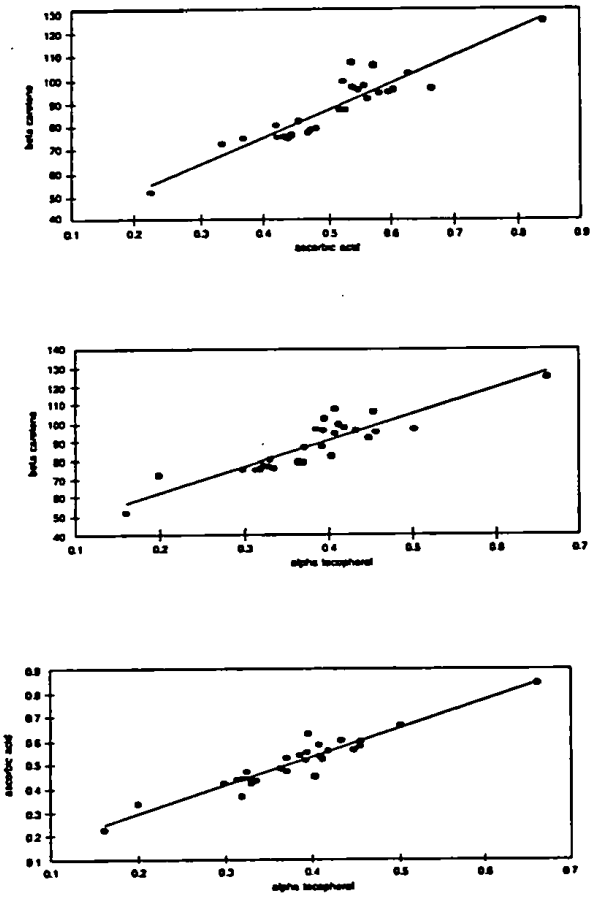


Fig. 3. Correlations among the three antioxidant vitamins studied.

The levels of all three antioxidant vitamins were lower in asthmatic patients compared to controls. One possible explanation for the low levels of vitamins is that the chronic lung disease may have caused decreased dietary intake of vitamins. This seems unlikely, as none of the patients had any evidence of nutritional deficiency. A more likely explanation would be that these vitamins are consumed at an increased rate as a defense mechanism of the organism against the ongoing oxidative burden. This explanation is also not totally satisfactory, as no correlation was observed between any of the vitamins and TBARS, FEV1 or PaO_2. Furthermore, there was no recovery in the low vitamin levels after the hypoxia abated. There are probably some other factors involved that cause the decreases in antioxidant vitamins. The results of this study do not elucidate a definitive cause-effect relationship between the antioxidant vitamins and oxidative stress.

The number of studies that have investigated the relationship between lung functions and antioxidants is quite limited. Vitamin C has attracted relatively more attention in this regard. In accord with our study, Aderele et al.[27] showed that asthmatic children had significantly lower vitamin C levels than controls. Data about the effect of vitamin C on lung function are contradictory, with some showing improvement[28-31] and some showing no effect[32-34]. Two recent studies investigated the role of dietary antioxidants using a questionnaire-based methodology[19,35]. Dow et al.[19] reported that dietary in take of vitamin E may influence lung function inthe elderly, but failed to find such an effect for vitamin C. Soutar et al.[35], in contrast, found that low intake of vitamin C, but not of β carotene or vitamin E, is associated with increased bronchial reactivity.

The imbalance between antioxidant and prooxidant forces has recently been shown in an animal model of asthma[18]. Investigators have shown that vitamin E and ascorbic acid are decreased by 8-and 4-folds in the bronchoalveolar lavage fluid of sensitized animals, and that these decreases are accompanied by a 2.4-fold higher concentration of lipid peroxidation products. The findings of this study support the idea that there is in fact a strong relationship between antioxidant vitamins and oxidant stress.

The observation of very strong correlations among all three antioxidant vitamins in our study strongly suggests that their involvement is most likely mediated via the same mechanism. Our study raises the interesting question of whether or not vitamin supplementation could be of any value in prevention or treatment of childhood asthma, especially in the early stages of disease. Animal studies are now under way to provide some clues to this question.

REFERENCES

1. Barnes PJ. Reactive oxygen species and airway inflammation. Free Radic Biol Med 1990; 9: 235-243.
2. Lansing MW, Mansour E, Ahmet A, et al. Lipid mediators contribute to oxygen radical induced airway responsiveness in sheep. Am Rev Respir Dis 1991; 144: 1291-1296.
3. Lansing MW, Ahmet A, Cortes A, et al. Oxygen radicals contribute to antigen induced airway responsiveness in conscious sheep. Am Rev Respir Dis 1993; 147: 321-326.
4. Postma DS, Renkema TE, Noordhoek JA, et al. Association between nonspecific bronchial hyperreactivity and superoxide anion production by polymorphonuclear leukocytes in chronic air-flow obstruction. Am Rev Respir Dis 1988; 137: 57-61.

5. Calhoun WJ, Bush RK. Enhanced reactive oxygen species metabolism of airspace cells and airway inflammation follow antigen challenge in human asthma. J Allergy Clin Immunol 1990; 86: 306-313.
6. Barnes PJ, Rhoden KJ. The effect of oxygen derived free radicals on airway smooth muscle responses. Br J Pharmacol 1987; 90 (Suppl): 142 P.
7. Renkema TE, Postma DS, Noordhoek JA, et al. Association between bronchial hyperreactivity and superoxide anion production by polymorphonuclear leukocytes in chronic airway obstruction. Agents Actions 1989; 26: 52-54.
8. Masahiko K, Nakano M, Morikawa A, et al. Ability of polymorphonuclear leukocytes to generate active oxygen species in children with brnochial asthma. Int Arch Allergy Appl Immunol 1991; 95: 17-22.
9. Jarjour NN, Calhoun WJ. Enhanced production of oxygen radicals in asthma. J Lab Clin Med 1994; 123: 131-137.
10. Meltzer S, Goldberg M, Lad P, Easton J. Superoxide generation and its modulation by adenosine in the neutrophils of subjects with asthma. J Allergy Clin Immunol 1989; 83: 960-966.
11. Cluzel M, Damon M, Chanez P, et al. Enhanced alveolar cell luminal-dependent chemiluminescence in asthma. J Allergy Clin Immunol 1987; 80: 195-201.
12. Calhoun WJ, Reed HE, Moest DR, Stevens C. Enhanced superoxide production by alveolar macrophages and air-space cells, airway inflammation, and alveolar macrophage density changes after segmental antigen bronchoprovocation in allergic subjects. Am Rev respir Dis 1992; 145: 317-325.
13. Jarjour NN, Busse WW, Calhoun WJ. Enhanced production of oxygen radicals in nocturnal asthma. Am Rev Respir Dis 1992; 146: 905-911.
14. İnan C, Kılıç I, Kılınç K, et al. The effect of high dose antenatal Vitamin E on hypoxia induced changes in newborn rats. Pediatr Res 1995; 38: 1-5.
15. Owen S, Pearson D, Suarez Mendez V, et al. Evidence of free radical activity in asthma. N Engl J Med 1991; 325: 586-587.
16. Rahman I, Morrison D, Donaldson K, MacNee W. Systemic oxidative stress in asthma, COP, and smokers. Am J Respir Crit Care Med 1996; 154: 1055-1060.
17. Chilvers ER, Garratt H, Whyte MK, et al. Absence of circulating products of oxygen derived free radicals in acute severe asthma. Eur Respir J 1989; 2: 950-954.
18. Shvedova AA, Kisin ER, Kagan VE, Karol H. Increased lipid peroxidation and decreased antioxidants in lungs of guinea pigs following an alergic plmonary response. Toxicol Appl Pharmacol 1995; 132: 72-81.
19. Dow L, Tracey M, Villar A, et al. Does dietary intake of vitamins C and E influence lung function in older people? Am J Respir Crit Care Med 1996; 154: 1401-1404.
20. Monteleone CA, Sherman AR. Nutrition and asthma. Arch Intern Med 1997; 157: 23-34.
21. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. National Heart Lung and Blood Institute/World dHealth Organization Workshop Report. National Institutes of Health Publication number: 95-3659. January 1995.
22. Wade CR, van Rij AM. Plasma thiobarbituric acid reactivity: reaction conditions and the role of iron, antioxidants and lipid peroxy radicals on the quantitation of plasma lipid peroxides. Life Sci 1988; 43: 1085-1093.
23. Desai ID. Vitamin E analysis methods for animal tissues. Methods Enzymol 1984; 105: 138-147.
24. Neeld JB, Pearson WN. Macro- and micromethods for the determination of serum vitamin A using trifluoroacetic acid. J Nutr 1963; 79: 454-462.
25. Loerch JD, Underwood BA. Vitamin A determinations in human blood: analysis of methodology. XIth International Congress of Nutrition, Rio de Janeiro, Brazil 1978.
26. Czajka-Narins DM. Nutrition. In: Tietz NW (ed). Textbook of Clinical Chemistry (3rd ed). Philadelphia: WB Saunders Co; 1987: 513-514.
27. Aderele WI, Ette IS, Oduwole O, Ikpeme SJ. Plasma vitamin C (ascorbic acid) levels in asthmatic children. Afr J Med Sci 1985; 14: 115-120.
28. Schwartz J, Weiss ST. Relationship between dietary vitamin C intake and pulmonary function in the first National Health and Nutrition Examination Survey (NHANES 1). Am J Clin Nutr 1994; 59: 110-114.
29 Schachter EN, Schlesinger A. The attenuation of exercise induced bronchospasm by vitamin C. Ann Allergy 1982; 49: 146-151.
30. Zuskin E, Lewis AJ, Bouhuys A. Inhibition of histamine-induced airway constriction by vitamin C. J Allergy Clin Immunol 1973; 51: 218-226.
31. Bucca C, Rolla G, Oliva A, Farina JC. Effect of vitamin C on histamine bronchial responsiveness of patients with allergic rhinitis. Ann Allergy 1990; 65: 311-314.
32. Ting S, Mansfield LE, Yarbrough J. effects of vitamin C on pulmonary functions in asthma. J Asthma 1983; 20: 39-42.
33. Kordansky DW. Rosenthal RR, Norman PS. The effect of vitamin C on antigen induced bronchospasm. J Allergy Clin Immunol 1979; 63: 61-64.
34. Malo JL, Cartier A, Pineau L, et al. Lack of acute effects of vitamin C on spirometry and airway responsiveness to histamine in subjects with asthma. J allergy Clin Immunol 1986; 78: 1153-1158.
35. Soutar A, Seaton A, Brown K. Bronchial reactivity and dietary antioxidants. Thorax 1997; 52: 166-170.

Iron status in breast-fed full-term infants

Ahmet Arvas[1], Yusuf Elgörmüş[1], Emel Gür[1], Müjgan Alikaşifoğlu[1], Ahmet Çelebi[1]

[1]Department of Pediatrics, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

SUMMARY: Arvas A, Elgörmüş Y, Gür E, Alikaşifoğlu M, Çelebi A. Iron status in breast-fed full-term infants. Turk J Pediatr 2000; 42: 22-26.

The aim of this study was to evaluate the iron status of full-term babies breast-fed exclusively for four months and the importance of iron supplementation.

One hundred sixteen term infants followed up since the newborn period by a well baby clinic were included in the study. Iron deficient and/or anemic infants were excluded from the study at four months. Some of the infants (51) were later given appropriate complementary food besides breast-feeding (Group A) and some (42) were given ferrous sulfate (1 mg/kg/d) (Group B). Blood count and serum iron and ferritin measurements were done at four and six months of age.

At the 4th month, iron deficiency was found in 23 (19.8%) infants, 11 of which had iron deficiency anemia. At the 6th month, 23 (45%) infants in Group A were iron deficient and 11 (21.6%) of them had iron deficiency anemia. In Group B, three (7.1%) infants were iron deficient and one (2.4%) of them also had iron deficiency anemia ($p < 0.0001$).

Significant iron deficiency and iron deficiency anemia have been found in four-month-old exclusively breast-fed full-term infants. It is observed that complementary food alone is insufficient; there is need for iron supplementation.

Key words: iron deficiency anemia, exclusive breast feeding, full-term infant, iron supplementation.

Iron deficiency anemia (IDA) is a common problem, especially in developing countries[1-3]. Usually in infants, iron deficiency anemia is seen between the 6th-24th months. It may occur for the following reasons: reduction of iron stores accummulated by the infant from the mother during intrauterine life by active transportation after the first months of life, foods unsupplemented with iron or intake of foods impairing iron absorption and increase in iron requirement during the rapid growth of the infant, and iron deficiency due to blood loss[4]. Iron deficiency (ID) and iron deficiency anemia may cause growth and development retardation and psychomotr disorders. Thus, prophylactic management and treatment have gained importance; however, the initial time of iron supplementation is controversial[5-7].

Breast milk contains small amounts of iron. Since its bioavailability is high, breast-feeding is important in prevention of iron deficiency anemia in early infancy. What remains controversial, however, is for how long exclusive breast-feeding is sufficient in meeting the nutritional requirements of an infant[1,8,9].

We designed this study in our well baby unit to evaluate the iron status of term infants who were followed from birth and were exclusively breast-fed for four months and to determine whether, after four months, iron supplementation is beneficial or not.

Material and Methods

One hundred and sixteen full-term infants born at the Department of Obstetrics of Cerrahpaşa Medical Faculty of İstanbul University and followed up between February-August 1997 at the Social Pediatrics Unit of the Pediatric Hospital were included in the study. All of them were exclusively breast-fed for four months. All of the infants were over 2500 g at birth. There was no perinatal or postnatal problem (i.e., no major congenital anomalies, no hemorrhage, transfusion, delayed cord clamping or infection).

None of the mothers had hypertension, chronic diseases, preeclampsia, or ablatio placentae. The families were informed about the study and their consent obtained. At the 4th month venous blood was drawn. Hemogram was done by cell counter analysis method (Coulter Micro Diff 18, Miami, USA). Serum iron (SI) and total iron binding capacity (TIBC) were measured by the colorimetric method (Iron/TIBC Reagent set-pointer Scientific Inc.). Serum ferritin (SF) was measured by radioimmunoassay method (Active™ Ferritin, Diagnostic Systems Laboratories-3000, Inc., USA).

Hemoglobin (Hb) < 9.5 g/dl, mean corpuscular volume (MCV) < 74 fl and SF < 12 ng/ml were the criteria for iron deficiency anemia. Hb > 9.5 g/dl and SF < 12 ng/ml were considered as iron deficiency[10].

Ferrous sulfate (6 mg/kg/d) was started in infants having these parameters and they were removed from the study. After the 4th infants (51) with even registration numbers were given complementary food besides breast-feeding (Group A). The other infants (42) with odd registration numbers were given ferrous sulfate (1 mg/kg/d) besides complementary food and breast-feeding (Group B). The infants of both groups were fed the same complementary foods in similar volumes following one week intervals. A cup of fruit juice (100 cc apple or carrot) has 0.1-0.3 mg elementary Fe, a cup of yogurt (150 g) has 0.15 mg elementary Fe and a plate of vegetable puree has 0.5-0.7 mg elementary Fe. At the 6th month, a venous blood sample was drawn and all parameters determined at the 4th month were repeated. Hb < 11 g/dl, MCV < 70 fl and SF < 12 ng/ml were accepted as iron deficiency anemia and Hb > 11 g/dl with SF < 12 ng/ml were accepted as iron deficiency[10,11].

Chi-square (χ^2) test, Student's-t test and paired and unpaired t test for statistical analysis were performed using statistical program of SPSS for Windows for 6.1.

Results

Fifty-eight of 116 infants included in the study were male and 58 were female. Educational status of their mothers was as follows: 16.8 percent literate or primary school graduate, 60.1 percent secondary school graduate, 23.1 percent university graduate; 0.7 percent of the families were in the lower income group, 95.8 percent were in the middle and 3.5 percent were in the higher income group.

Demographic features and hematological values of the infants are shown in Table I.

Table I. Demographic Characteristics and Hematological Findings at 4th Month

Number (n)	116	Hb (g/dl)	10.1 (0.7)*
Girls	58	Hct (%)	30.0 (1.9)*
Boys	58	MCV (fl)	77.6 (3.2)*
Mother's age (y)		RDW (%)	14.6 (0.8)
Range	19-37	SI (µg/dl)	39.1 (15.4)*
Mean (SD)	27.7 (4.4)	SF (ng/dl)	29.3 (18.2)*
Birth weight (g)		TIBC (µg/dl)	349.2 (52.6)
Range	2510-4400	Iron deficiency	23 (19.8)**
Mean (SD)	3299.2 (405.9)	Iron deficiency anemia	11 (9.5)**
Four-month weight (g)			
Range	5900-9750		
Mean (SD)	7138.5 (676.8)		

* Mean (SD).
** Numbers in parentheses represent percentages.
Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; RDW: red blood cell distribution width; SI: serum iron; SF: Serum ferritin; TIBC: total iron binding capacity.

Evaluation of Infants at 4th Month: The distribution of age was 118-124 days (mean 122.6) at the time of examination. Iron deficiency was found in 23 (19.8%) of the 116 infants and iron deficiency anemia in 11 (95%) of these. There was a significant correlation between the educational level of the mothers and iron deficiency/iron deficiency anemia ($p = 0.015$). While nine infants (37.5%) of the 24 literate or primary school graduate mothers were iron deficient and five (20.8%) had iron deficiency anemia, just one infant (2.03%) of the 33 university graduate mothers was iron deficient. Iron deficiency anemia was more frequent in the lower income group ($p = 0.01$). No significant correlation was determined between the hematological values (serum iron, serum ferritin, total iron binding capacity, mean corpuscular volume, hemoglobin, red cell distribution witdth), birth weight, four-month weight and age of mother ($p > 0.05$).

Evaluation of Infants at 6th Month: 51 of the 93 infants remaining in the study were classified as Group A and 42 infants as Group B. The distribution of age was 179-184 days

(mean 182.2) and 179-186 days (mean 182.8) in Groups A and B, respectively. There was no significant difference between the mother's age, the distribution of age, the educational status of the mothers, income level of the families, birth weight and four-month weight within the two groups ($p > 0.05$). However, the mean weight of infants at six months in Group B was higher than in Group A ($p = 0.018$). Iron deficiency was found in 23 (45%) infants and iron deficiency anemia in 11 of the 23 infants (21.6%) in Group A. In Group B, deficiency was found in three (7.1%) infants and iron deficiency anemia in 1 (2.4%) of those.

Hemoglobin, hematocrit, mean corpuscular volume, serum iron and serum ferritin in Group were higher than in Group A ($p < 0.0001$). Red cell distribution width (RDW) and total iron binding capacity were higher in Group A ($p < 0.01$, $p = 0.005$, respectively). Hematological values at the 6th month are shown in Table II.

Evaluation of Groups at the 4th and 6th Month: In the 6th month, hemoglobin (Hb) and hematocrit (Hct) values when compared to those at the 4th month were not significant in Group A ($p > 0.05$). Mean corpuscular volume, serum iron and serum ferritin values at the 6th month, were significantly decreased ($p < 0.0001$, $p = 0.29$, $p < 0.0001$, respectively). In Group B at the 6th month, hemoglobin, hematocrit, serum iron and serum frritin when compared to the 4th month were significantly increased ($p < 0.0001$, $p < 0.0001$, $p = 0.001$, $p = 0.002$, respectively).

Hemotological values at the 4th and 6th month are shown in Table III.

Table III. Hematological Findings of Groups at 4th Month and 6th Month

		4th Month*	6th Month*	p
Group A (n = 51)	Hb (g/dl)	10.2 (0.5)	10.5 (1.0)	> 0.05
	Hct (%)	30.6 (0.8)	30.7 (2.9)	> 0.05
	MCV (fl)	78.7 (2.8)	74.7 (3.9)	< 0.0001
	RDW (%)	14.5 (0.8)	15.3 (0.8)	> 0.05
	SI (µg/dl)	42.6 (12.7)	37.0 (12.7)	0.029
	SF (ng/dl)	35.0 (19.2)	16.6 (9.2)	< 0.0001
	TIBC (µg/dl)	331.0 (51.2)	370.3 (46.2)	< 0.0001
Group B (n = 42)	Hb (g/dl)	10.3 (0.5)	11.6 (0.8)	< 0.0001
	Hct (%)	30.6 (1.9)	33.2 (2.3)	< 0.0001
	MCV (fl)	77.9 (2.7)	77.7 (2.4)	> 0.05
	RDW (%)	14.7 (0.8)	14.1 (0.7)	> 0.05
	SI (µg/dl)	40.9 (18.3)	61.3 (29.9)	0.001
	SF (ng/dl)	33.6 (13.3)	49.9 (29.1)	0.002
	TIBC (µg/dl)	347.5 (48.2)	350.0 (58.4)	> 0.05

* Mean (SD).

Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; RDW: red blood cell distribution width; SI: serum iron; SF: Serum ferritin; TIBC: total iron binding capacity.

Discussion

Iron deficiency and iron deficiency anemia are more common in developing countries[12,13]. A study in our country performed among infants who were breast-fed for the first four months, who took appropriate complementary food but no iron supplementation after four months and who were followed up until the end of the first year determined iron deficiency in 13.9 percent of cases[14]. It is reported that anemia in pregnancy may affect the infant's iron stores negatively even though active transportation of iron is peresnt. Hussain et al.[15] and Singla et al.[16] reported that cord blood hemoglobin, hematocrit, serum ferritin and serum iron values are low in infants of anemic mothers in comparison to infants of mothers without anemia. Tekinalp et

Table II. Heatological Findings of Groups at 6th Month

	Group A	Group B		Group A*	Group B*	p
Number (n)	51	42	Hb (g/dl)	10.5 (1.0)	11.6 (0.8)	< 0.0001
Girls	26	24	Hct (%)	30.7 (2.9)	33.2 (2.3)	< 0.0001
Boys	25	18	MCV (fl)	74.7 (3.9)	77.7 (2.4)	< 0.0001
Iron deficiency n (%)	23 (45)	3 (7.1)	RDW (%)	15.3 (0.8)	14.1 (0.7)	< 0.001
			SI (µg/dl)	37.0 (12.7)	61.3 (29.9)	< 0.0001
Iron deficiency anemia n (%)	11 (21.6)	1 (2.4)	SF (ng/dl)	16.6 (9.2)	49.9 (29.1)	< 0.0001
			TIBC (µg/dl)	370.3 (46.2)	350.0 (58.4)	< 0.005

* Mean (SD).

Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; RDW: red blood cell distribution width; SI: serum iron; SF: serum ferritin; TIBC: total iron binding capacity.

al.[17] found positive correlation between maternal and neonatal iron stores. In our study, we did not find gestational and postnatal maternal hematological values. We also did not determine how much and for how long iron supplementation was taken by pregnant women, even though obstetricans suggest it in Turkey. In one study[18], iron deficiency during pregnancy was found to be 51 percent. However, we still believe that iron deficiency and iron deficiency anemia in infants at the 4th month which persist at the 6th month in spite of appropriate complementary food are a result of deficient stores because of gestational anemia. In Turkey, there is no iron-supplemented food product aside from formula, so complementary foods cannot prevent iron deficiency.

Even though breast-feeding is an ideal source of nutrition and its low iron content has a high bioavailability, for how long it is sufficient in meeting the iron requirement of infants is controversial. McMillian et al.[19] and Saarinen[20] reported that breast-feeding until the 6th month does not result in anemia, while Garry et al.[9], Duncan et al.[8] and Kim et al[21]. stressed the need for supplementary iron at six months. Calvo et al.[1] found anemia in 27.8 percent of the 9th month breast-fed infants, but 7.1 percent of the anemic had taken iron-fortified formulas which thus suggested iron supplementation after four months. While Pizarra et al.[22] suggested iron supplementation at the 6th month for infants who were exclusively breast-fed for nine months, Pisacane et al.[23] found no anemia in infants who were exclusively breast-fed for seven months or more. The American Academy of Pediatrics Nutritional Committee has suggested 1 mg/kg/d iron supplementation in full-term infants starting after the 4th month of life[6]. In fact, in our stduy the rates of iron deficiency and iron deficiency anemia were low (7.1% and 2.4%, respectively) in infants given supplementary iron after the 4th month (Group B).

If complementary food is given to infants before the 6th month, it will affect iron absorption in human milk negatively. Thus, it is believed human milk is enough for the first six months[20,22]. However, in most countries, exclusive breast-feeding is not done for long because of urbanization, traditional events and educational failure regarding the importance of human milk, etc. The percentage of exclusively breast-fed infants in the first three months is 14 percent in Turkey[24]. In our unit, this percentage is 40 percent despite intensive efforts to educate mothers. After the 4th month we give complementary food in addition to breast-feeding in our wall baby unit. All of the infants were fed the same complementary food. None of the infants included in this study were exclusively breast-fed or given bovine milk or formula after the 4th month.

In conclusion, in our study iron deficiency and iron deficiency anemia in infants exclusively breast-fed for the first four months were found to be higher when compared to previous reports. We think this was caused by gestational anemia, even though we did not know the iron status or hematological values of the mothers. Persistence of iron deficiency and iron deficiency anemia even after appropriate complementary food raised the need for supplementary iron in full-term infants. Since it is obvious that gestational anemia contributes to a great extent to anemia in early infancy, iron supplementation in pregnancy and exclusive breast-feeding for the first six months must be suggested in developing countries. However, when the iron status in mothers is not known and complementary foods are begun at the 4th month (as in most countries), it is more suitable to give iron supplementation at the 4th month and preferably, even before.

REFERENCES

1. Calvo EB, Galindo AC, Aspres NB. Iron status in exclusively breast-fed infants. Pediatrics 1992; 90: 375-379.
2. Calvo EB, Gnazo N. Prevalence of iron deficiency in children aged 9-24 months from large urban area of Argentina. Am J Clin Nutr 1990; 52: 534-540.
3. Cook JD, Skikne BS. Estimates of iron sufficiency in the US population. Blood 1986; 68: 726-731.
4. Oski FA, Landaw SA. Inhibition of iron absorption from human milk by baby food. Am J Dis Child 1980; 134: 459-460.
5. Aukett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increased weight gain and psychomotor development. Arch Dis Child 1986; 61: 849-857.
6. Committee on Nutrition, American Academy of Pediatrics. Iron supplementation for infants. Pediatrics 1976; 58: 765-771.
7. Durie PR. Iron supplementation and the breast-fed infants. J Pediatr Gastroenterol Nutr 1985; 4: 344-345.
8. Duncan B, Schifmann RB. Iron and exclusively breast-fed infants from birth to six months. J Pediatr Gastroenterol Nutr 1985; 4: 421-425.
9. Garry PJ, Owen GM, Hooper EM. Iron absorption from human milk and formula with and without iron supplementation. Pediatr Res 1981; 15: 822-828.
10. Lanzkowsy P. Manual of Pediatric Hematology and Oncology (2nd ed). New York: Churchill Livingstone: 1995: 630-631.

11. Nutritional anemia: Report of a WHO group of experts. World Health Organ Tech Rep Ser 1972; 503: 1-29.
12. Dallman PR, Siimes MA. Iron deficiency in infancy and childhood. Am J Clin Nutr 1980; 33: 86-118.
13. Dalman PR, Yip R. Prevalence of anemia in the United States, 1976-1980. Am J Clin Nutr 1984; 39: 437-445.
14. Çağlar MK, Cengiz AB, Özsan S, Kahraman H. Süt çocukluğu döneminde demir desteği uygulaması ve sonuçları. Türk Clin J Pediatr 1995; 4: 133-136.
15. Hssain MA, Gaafar TH, Laulicht M. Relation of maternal and cord blood serum ferritin. Arch Dis Child 1977; 52: 782-784.
16. Singla PN, Tyagi M, Shankar R. Fetal iron status in maternal anaemia. Acta Paediatr 1996; 85: 1327-1330.
17. Tekinalp G, Oran O, Gürakan B. Relationship between maternal and neonatal iron stores. Turk J Pediatr 1996; 38: 439-445.
18. Çepni İ, Gezer A, Madazlı R, Altınok T, İdil M, Aksu MF. Gebelikte Anemi. Kesitsel bir çalışma. İst J Gynecol Obstet 1997; 1: 88-92.
19. McMillian JA, Landraw SA, Oski FA. Iron sufficiency in breast-fed infants and the availability of iron from human milk. Pediatrics 1976; 58: 686-690.
20. Saarinen UM. Need for iron supplementation in infants on prolonged breast feeding. J Pediatr 1976; 93: 177-180.
21. Kim SK, Cheong WS, Jun YH, Chai JW, Son BK. Red blood cell indices and iron status according to feeding practices in infants and young children. Acta Paediatr 1996; 85: 139-144.
22. Pizarro F, Yip R, Dallman PR, Olivares M, Hertampf E, Walter T. Iron status with different feeding regimen. Relevance to screening and prevention of iron deficiency. J Pediatr 1991; 118: 687-692.
23. Pisacanne A, Vizia BD, Valiante A, et al. Iron status in breast-fed infants. J Pediatr 1995; 127. 429-431.
24. The State of the World's Children in 1998: Oxford Press for UNICEF.

Depression in children with hemophilic arthropathy and poliomyelitis: a preliminary report

Reyhan Çeliker[1], Yeşim Gökçe Kutsal[1], Belma Öy[2], Özlem Onur[1], Aytemiz Gürgey[3]

[1]Department of Physical Medicine and Rehabilitation, Hacettepe University Faculty of Medicine, [2]Department of Child Psychiatry, Dr. Sami Ulus Children's Hospital, and [3]Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara,Turkey

SUMMARY: Çeliker R, Gökçe-kutsal Y, Öy B, Onur Ö, Gürgey A. Depression in children with hemophilic arthropathy and poliomyelitis: a preliminary report. Turk J Pediatr 2000; 42: 27-30.

The aim of this study was to evaluate children with chronic disorders like hemophilia and poliomyelitis from the psychological perspective, to determine the frequency of depression, to identify the risk factors and to investigate the relation between disability and depression. Thirty-five patients with disability due to poliomyelitis and 12 patients with hemophilic arthropathy were included in the study. Thirty-six healthy children from the district schools served as controls. The Children's Depression Inventory (CDI) was used to assess the extent of depression. For the hemophilia group, joint scores proposed by the World Federation of Hemophilia were used to assess the degree of joint involvement. The pliomyelitis group was evaluated according to the level of ambulation and the need for orthoses. The CDI score was 10.57 ± 5.87 in the poliomyelitis group, 11.00 ± 5.64 in the hemophilic arthropathy group and 8.39 ± 3.78 in the control group, but the difference was not statistically significant. Four of 35 patients with poliomyelitis (11.4%) and two of 12 hemophilic arthropathy patients (16%) exhibitea depression. None of the children in the control group had depression. Since depression interferes with both medical compliance and rehabilitation potential, early diagnosis and treatment is important. Therefore, evaluation of the pyschological status of chronically ill children must be a part of the rehabilitation program.

Key words: depression, hemophilia, poliomyelitis.

Psychosocial states play an important role in the outcome of chronic diseases. Therefore, during the past decade, psychiatric disturbances chronically ill people, especially depression, has been the focus of concern[1,2].

Depression is highly prevalent in adults with a chronic or disabling disease; however, people tend to overlook the psychological status of sick children. Chronic medical problems promote a state of anxiety and depression in children. There are various methods to assess the depressive symptoms in children. The Children's Depression Inventory (CDI) is the most common self-report inventory used to determine childhood depression. Several studies in literature have shown that CDI is a reliable method[3].

Depressive symptoms have been widely studied in postpoliomyelitis patients; however, psychosocial disturbances and adaptation mechanisms to initial losses in young acute paralytic polio survivors are subtle[4]. Reports on the psychosocial effects of hemophilia are conflicting. While early papers report severe adjustment problems[5,6], more recent ones report no difference between children with hemophilia and the general population[7].

In this study we aimed to describe the prevalence of depression among children with hemophilic arthropathy and poliomyelitis. The demographic characteristics of depressed and nondepressed subjects, the extent of arthropathy in the hemophilic arthropathy group and the level of ambulation and need for orthoses in the poliomyelitis group were also investigated.

Material and Methods

Thirty-five children with disability due to poliomyelitis and 12 children with hemophilic

arthropathy who were followed by the Department of Physical Medicine and Rehabilitation were included in the study. Thirty-six healthy children identical in age, social class, birth order and family size comprised the control group.

All subjects were interviewed and examined by the same physician. For the hemophilia group, each patient was assessed by scores proposed by the World Federation of Hemophilia including joint scores, pain scores, bleeding scores[8] and Pettersson's radiological score[9,10]. For the poliomyelitis group, patients were evaluated for muscle strength, level of ambulation and the need for orthosis. The Children's Depression Inventory was administered to assess depression. CDI is a self-report questionnaire which has been proven valid and reliable in the Turkish pediatric population[11]. It includes 27 items, each rated on a 0-2 point scale, and reflects the cognitive, affective and behavioral symptoms of depression. Each item is expressed in three alternate statements and the subject is asked to choose the one that best describes the way he or she has been feeling during the preceding two weeks[3,12].

For statistical analysis, Student's t-test, Pearson's correlation matrix, one way ANOVA and chi-square tests were used.

Results

The mean ages of children with hemophilia and poliomyelitis were 10.75 ± 1.42 and 10.57 ± 5.87 years, respectively. In the hemophilia group, all 12 children were male, while in the poliomyelitis group 22 patients were male and 13 female. Thirty male and 6 female healthy children, with a mean age of 11.01 ± 1.56 years, comprised the control group. The mean durations of the disease for the poliomyelitis and hemophilic arthropathy patients were 9.54 and 9.83 years, respectively (Table I).

The mean CDI scores were 11.0 ± 5.36 and 10.57 ± 5.87 for the hemophilia and poliomyelitis groups, respectively (Table II). These scores were higher than the mean CDI score of the control group (8.39 ± 3.78), but the difference was not statistically significant for either group ($p > 0.05$). The cut-off score for CDI was 19. Four of 35 patients with poliomyelitis (11.4%) and two of those with hemophilic arthropathy (16%) had CDI joint scores greater than 19. Depression in the hemophilic arthropathy and poliomyelitis patients was more frequent than in the healthy control group ($p < 0.05$). No correlation was found between CDI scores and the duration of the disease for either group ($p > 0.05$). Table III shows the mean joint scores of the hemophilic patients. No correlationn was found between the joint scores and the CDI scores for the hemophilic patients. Among 35 poliomyelitis patients, 10 were wearing orthopedic shoes, 13 were using a short leg walking brace and 12 were using a long leg walking brace. Thirty-three of 35 patients were independent in ambulation and two were dependent. When CDI scores of these patients were compared with respect to the need for orthosis, CDI scores of the patients using a long leg walking brace were higher than those of patients who were using a short leg walking brace or wearing orthopedic shoes ($p < 0.05$).

Table I. Mean Age, Sex Ratio and Mean Duration of Disease in the Patient and Control Groups

	Hemophilia group (n = 12)	Poliomyelitis group (n = 35)	Control group (n = 36)
Age (year)	10.75±1.42	10.57±5.87	11.01±1.56
Male/female	12/0	22/13	30/6
Duration of disease (year)	9.83	9.54	

Table II. Children's Depression Inventory (CDI) Scores of Poliomyelitis, Hemophilia and Control Groups

	Hemophilia group	Poliomyelitis group	Control group	p value
CDI scores	11.00±5.36	10.57±5.87	8.39±3.78	> 0.05

Table III. Assessment of the Joints Using Joint Scores in Hemophilic Arthropathy Patients

	Mean	Standard deviation	Min.	Max.	Range
Physical examination	5.08	1.83	1	8	0-12
Pain	0.92	1.08	0	3	0-3
Bleeding	3.00	0.00	3	3	0-3
Pettersson score	5.83	3.30	1	10	0-13

Discussion

Although work in the field of childhood depression is relatively new, a considerable amount of knowledge has already accumulated in the literature. Differences involving depression in children and in adults have been found. Data for adults indicate that depression is more prevalent in women than in men, whereas studies involving prepubertal children have not revealed consistent sex differences in

the prevalence of major depression.Some of the serious concomitants of depression, such as suicide, are less evident in children[13].

Children with chronic health conditions have long been considered at substantial risk for psychosocial morbidity, especially depression. There are a wide variety of reasons to expect an increased risk of depression among these children. First, many chronic health impairments are associated with chronic or recurrent episodes of pain or with an acutely diminished or altered physiological function, which may promote the state of anxiety and depression. Also, the peresence of a chronic condition may limit or alter social interactions[1].

The Children's Depression Inventory (CDI) is the most common self-report inventory used for determining childhood depression. It is essentially a downward extension of the Beck Depression Inventory[13]. Several additional items are included that attempt to assess areas of school and social/peer relations[14]. In literature, several reports exist about the normative and reliability data of the CDI[15-17]. In a study carried out on 432 Turkish children, the CDI was found to be highly reliable and valid[11].

There are conflicting data about the psyschosocial effects of hemophilia. In literature, there are some reports about adjustment problems and poor social functioning in hemophilic patients[5,6]. However, others reported little or no difference between the hemophilic children and the normal population with respect to social adjustment and personality[7]. More recent studies focused on the impact of HIV infection on the psyschological status of hemophilic patients. Logan et al.[18] reported that children with hemophilia were no more disturbed psychologically than their diabetic or healthy peers, despite the identification of HIV infection. In another study among adolescents with hemophilia, the mean scores for anxiety and depression inventories did not differ significantly from those of the reference group[19]. However, another study showed higher depressive scores in HIV (+) adult hemophilic men compared to HIV (-) patients[20].

In our study, the mean CDI scores of the children with hemophilia were greater than those of the control group. However, this difference was not statistically significant. Also, no correlation was found between CDI scores and the joint scores of the hemophilic patients.

Depression associated with postpoliomyelitis syndrome has been widely studied in the literature. Most of the patients successfully adapt to their initial losses from acute polio, but later, newly developing disabilities are accompanied by stress, depression and anxiety. Tate et al.[4] reported elevated distress and depression in patients with postpoliomyelitis syndrome. In their study, it was shown that depressed patients experienced more accentuated physical deterioration, had a higher number of somatic complaints and reported a greater increase in pain. In another study, postpolio patients had more depressive symptoms than the control group; however, scores in activities of daily living were not related to depression. Rather, work, leisure, recreation, socialization and community interactions are the factors that mostly contributed to depression[21]. Berlly et al.[22] reported mild-to-moderate depressive symptoms in 27 percent of the postpolio group and in none of the controls.

Although acute poliomyelitis has been eradicated in most of the developed countries, it is still an important cause of disability in underdeveloped countries. However, very few studies have been conducted about depression in acute poliomyelitis patients. In our study, we found that children with poliomyelitis had higher CDI scores than the control group, but the difference was not statistically significant. When CDI scores of these patients were compared with respect to the need for orthosis, CDI scores of the patients that were using a long leg walking brace were significantly higher compared to those who were using a short leg walking brace. This result suggests a correlation between the severity of the disability and the deegree of depression.

Since depression in a child with a chronic illness is an important handicap for the rehabilitation process, depressive symptoms must be recognized and treated immediately.

REFERENCES

1. Gortmaker SL, Walker DK, Weitzman M, Sobol AM. Chronic conditions, socioeconomic risks, and behavioral problems in children and adolescents. Pediatrics 1990; 85: 267-276.
2. Kovacs M, Gatsonis C, Paulauskas L, Richards C. Depressive disorders in childhood. Arch Gen Psychiatry 1989; 46: 776-782.
3. Saylor CF, Finch AJ Jr, Spirito A, Bennett B. The children's depression inventory: a systematic evaluation of psychometric properties. J Consulting Clin Psychol 1984; 52: 955-967.
4. Tate D, Kirsch N, Maynard F, et al. Coping with the late effects: differences between depressed and nondepressed polio survivors. Am J Phys Med Rehabil 1994; 73: 27-35.

5. Mattson A, Gross S. Adaptational and defensive behavior in young hemophiliacs and their parents. Am J Psychiatry 1966; 122: 1349-1356.

6. Boon RA, Roberts DF. The social impact of hemophilia. J Biosoc Sic 1970; 2: 237-264.

7. Steinhausen HC. Chronically ill and handicapped children and adolescents: personality studies in relation to disease. J Abnorm Chil Psychology 1981; 9: 291-297.

8. Gilbert MS. Prophylaxis. musculoskeletal evaluation. Semin Hematol 1993; 30 (Suppl): 3-6.

9. Erlemann R, Rosenthal H, Walthers EM, et al. Reproducibility of the Pettersson scoring system. An interobserver study. Acta Radiol 1989; 30: 147-151.

10. Petterson H. Radiographic scores and implications. Semin Hematol 1993; 30 (Suppl): 7-9.

11. Öy B. Children's depression inventory: a study of reliability and validity. Turk J Psychiatr 1991; 2: 132-136.

12. Kazdin AE. Childhood depression. J Child Psychol Psychiat 1990; 31: 121-160.

13. Kendall PC, Catwell DP, Kazdi AE. Depression in children and adolescents: assessment issues and recommendations. Cognitive Ther Research 1989; 13: 109-146.

14. Kovacs M. The Children's Depression Inventory (CDI). Psychopharmacol Bull 1985; 21: 995-998.

15. Smucker MR, Craighead WE, Craighead LW, Green BJ. Normative and reliability data for the Children's Depression Inventory. J Abnormal Child Psychol 1986; 14: 25-39.

16. Nelson WM 3d, Politano PM, Finch AJ Jr, Wendel N, Mayhall C. Children's Depression Inventory: normative data and utility with emotionally disturbed children. J Am Acad Child Adol Psychiat 1987; 26: 43-48.

17. Finch AJ Jr, Saylor CF, Edwards Gl Children's depression inventory: sex and grade norms for normal children. J Consulting Clin Psychol 1985; 53: 424-425.

18. Logan FA, Maclean A, Howie CA, et al. Psychological disturbance in chidren with hemophilia. Br Med J 1990; 301: 1253-1256.

19. Overby KJ, Lo B, Litt IF. Knowledge and concerns about acquired immunodeficiency syndrome and their relationship to behavior among adolescents with hemophilia. Pediatrics 1989; 83: 204-210.

20. Dew MA, Ragni MV, Nimorwicz P. Infection with human immunodeficiency virus and vulnerabilty to psychiatric distress. Arch Gen Psychiatry 1990; 47: 737-744.

21. Kemp BJ, Adams BM, Campbell LM. Depression and life satisfaction in aging polio survivors versus age-matched controls: relation to postpolio syndrome, family functioning, and attitude toward disability. Arch Phys Med Rehabil 1997; 78: 187-192.

22. Berly MH, Strauser WW, Hall KM. Fatigue in postpolio syndrome. Arch Phys Med Rehabil 1991; 72: 115-118.

Propranolol for primary and secondary propylaxis of variceal bleeding in children with cirrhosis

Şinasi Özsoylu[1], Nurten Koçak[2], Hülya Demir[2], Aysel Yüce[2], Figen Gürakan[2], Hasan Özen[2]

[1]Department of Pediatrics, Fatih University Faculty of Medicine, and [2]Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Ozsoylu Ş, Koçak N, Demir H, Yüce A, Gürakan F, Özen H. Propranolol for primary and secondary prophylaxis of variceal bleeding in children with cirrhosis. Turk J Pediatr 2000; 42: 31-33.

Variceal bleeding due to portal hypertension is a frequent and severe complication of cirrhosis in children as in adults. The prophylactic approach is important for these high mortality bleedings, both for the first and for recurrent attacks. Variceal bleeding/rebleeding rates were evaluated in sixty patients with cirrhosis who received 1-2 mg/kg/day propranolol p.o. for 1-14 years. According to Child-Pugh classification, 33 patients were Class A, 22 Class B, and five Class C. Patients were divided into two groups according to whether they had variceal bleeding before starting propranolol treatment (secondary prevention; 15 patients) or not (primary prevention; 45 patients). Seven (15.6%) of 45 patients experienced bleeding on propranolol therapy in the primary prevention group, while eight (53.3%) of 15 patients bled in the secondary prevention group ($p < 0.01$). Propranolol was found effective in primary and secondary prevention in Class A patients, while it was effective only for primary prevention in Class B and C patients. Propranolol administration is useful for preventing first and recurrent variceal bleeding in Class A cirrhotic patients. In Class B and C cirrhotic patients, it is effective only for preventing the first bleeding episode.

Key words: children, cirrhosis, variceal bleeding, propranolol, prophylaxis.

Variceal bleeding due to portal hypertension is a frequent and severe complication of cirrhosis in children as in adults. The prophylactic approach is important for these high mortality bleedings, both for the first and for recurrent attacks[1]. Nonselective β-adrenergic blocker drugs such as propranolol are widely used for this purpose, mostly in adults[2-8]. Data about the effect of β-blockers for prevention of variceal bleeding in cirrhotic children is limited. The aim of this study was to evaluate the effectiveness of propranolol for prevention of variceal hemorrhage in cirrhotic children.

Material and Methods

Sixty patients with portal hypertension and histopathologically proven cirrhosis, aged between two and a half years and 18 years (mean 9.9 ± 3.5 years), were evaluated in this study. Files of the patients diagnosed between 1982 and 1997 were retrospectively evaluated. All patients were given propranolol at a dose of 1-2 mg/kg/day p.o. bid and the dose was regulated according to a heart rate decrease of 25 percent from the baseline. Patients were divided into two groups: 45 children who had not bled prior to propranolol therapy (primary prevention; PP) and 15 children who had bled before the treatment (secondary prevention; SP). Additionally, patients were evaluated according to Child-Pugh classification[9]. Because we showed that propranolol was effective for lowering portal pressure[4], it would be unethical to not give propranolol to the control group. Parents as well as older children were strictly instructed to discontinue the drug when bleeding was observed. Patients were examined in the outpatient clinic every three months and hospitalized if they presented with hematemesis or melena. All bleeding episodes were recorded. Neither prophylactic nor therapeutic endoscopic sclerotherapy was used for the patients included in this study. The Sengstaken-Blakemore tube was replaced to stop bleeding when necessary

and blood transfusion(s) was given if indicated. Statistical evaluations were made using Fisher's exact and Kruskal-Wallis tests where appropriate. When comparing groups, patients in Child-Pugh Class B and C were considered together because of the relatively small number of patients in Child-Plugh Class C. A "p" value less than 0.05 was considered as significant.

Results

The patients were followed for one to 14 years (mean 5.5 ± 3.3, median 5 years). According to Child-Pugh classification[9], 33 patients (55%, mean age 9.8 ± 3.8 years) were Child-Pugh Class A, 22 (37%, mean age 10.0 ± 3.0 years) were Child-Pugh Class B and five (8%, mean age 10.0 ± 4.3 years) were Child-Pugh Class C. Mean follow up was 4.9 ± 2.3 years, 6.8 ± 4.3 years, and 3.4 ± 1.3 years, respectively, for the patients in Child-Pugh A, B and C Classes. The mean ages of the patients and mean follow-up duration were not statistically different between the three groups.

Among 45 patients in the PP group, only seven (15.6%) had vericeal bleeding under propranolol treatment. Eight out of 15 patients (53.3%) in the SP group experienced recurrent bleeding episode(s) under propranolol treatment ($p < 0.01$).

In Class A patients, two of 28 (7%) patients of the PP group and one of five (20%) patients in the SP group ($p > 0.05$) had a first bleeding episode. These rates were 29 (5/17) and 70 percent (7/10) with Child-Pugh Class B plus C patients ($p = 0.056$) (Table I).

Discussion

The purpose of drug therapy in portal hypertension is to obtain a sustained decrease in portal pressure. We showed for the first time that propranolol reduces portal pressure in children with portal hypertension[4] by decreasing portal blood flow through the blockage of $\beta_1+\beta_2$ adrenergic receptors[1,10]. obtaining a hepatic venous pressure gradient < 12 mmHg or a decrease of > 20 percent from its baseline level is known to be sufficient for preventing variceal hemorrhage[11].

It was shown that propranolol was efficient for preventing the first variceal bleeding in Child-Pugh A, B, and C patients[5-7]. In their placebo controlled study, Conn et al.[5] observed an overall bleeding rate of 3.9 percent 82/51) in patients receiving propranolol and of 21.6 percent (11/51) in the control group ($p = 0.01$). When subgroups of Child-Pugh classification were taken into consideration, propranolol was more effective than a placebo in Class B and C patients with cirrhosis ($p < 0.05$), whereas the difference between propranolol and placebo was not significant in patients with Class A cirrhosis. In a multicenter study with 174 patients who had not bled previously[6], propranolol treatment was compared with vitamin K. The overall bleeding rate was 18.8 percent in the treatment group and 30.3 percent in the control group ($p < 0.05$). A statistically significant result was obtained only in patients with Class A cirrhosis (12% in propranolol group vs 36% in the control group, $p = 0.01$). Pascal et al.[7] compared the efficacy of propranolol for preventing variceal bleeding with a placebo in 230 patients who had no previous bleeding. The bleeding rate in patients in the propranolol group was 17 percent. The cumulative percentage of patients free of bleeding two years after inclusion were 74 percent in the treatment group and 39 percent in the placebo group ($p < 0.05$). They classified their patients as those in good condition and those in poor condition, and the difference was

Table I. Effect of Propranolol in Patients with and without Prior Bleeding According to Child-Pugh Classification

	Patients class A		Patients class B+C		Total	
Propranolol therapy	Bled[a]	Not bled	Bled[b]	Not bled	Bled[c]	Not bled
Primary prevention	3 (7.1)*	26 (92.9)	5 (29.4)	12 (70.6)	7 (15.6)	38 (84.4)
Secondary prevention	1 (20)	4 (80)	7 (70)	3 (30)	8 (53.3)	7 (46.7)
Total	3 (9.1)	30 (80.9)	12 (44.4)	15 (55.6)	15 (33.3)	45 (66.7)

* Values are percentages.
[a] $p > 0.05$ (primary prevention vs secondary prevention).
[b] $p < 0.056$ (primary prevention vs secondary prevention).
[c] $p < 0.01$ (primary prevention vs secondary prevention).

significant in the patients in poor condition. The study populations of these three studies were adult patients. Addtionally, two meta-analyses also showed that propranolol therapy was effective in preventing first bleeding in adult patients with cirrhosis[12,13]. In our study, overall bleeding rate was 15.6 percent in PP patients, which was similar to previous studies[6,7]. It has also been shown that propranolol was more effective for PP than SP.

The efficacy of propranalol of recurrent variceal bleeding is controversial. Lebrec et al.[2] observed recurrent variceal hemorrhage in only one of 38 (3%) patients with compensated cirrhosis (72% Class A). Some other studies deny the efficacy of propranolol in preventing recurrent bleeding. Villeneuve et al.[8] reported recurrent bleeding in 76 percent of 42 patients (89% of whom were Class B and C) receiving the drug. Another study showed a recurrent bleeding rate of 46 percent in similar patients[3]. In our study, while propranolol was effective in SP in Class A patients (20% rebleeding rate), it was inefficient in Class B plus C patients (70% rebleeding rate). In an experimental study, it has been shown that early propranolol administration before collateral circulation development reduced the severity of portal hypertension and portal-systemic shunts in portal vein stenosed rats[14]. Escorcell et al.[15] demonstrade that β-blockers decreased portal pressure more in patients without rather than with varices.

Propranolol seems effective forr PP in all cirrhotic patients regardless of the severity of the disease, in other words, both in compensated and decompensated patients, when administered at appropriate doses. However, for SP it is effective in only Child-Pugh Class A patients, but not in the ones with signs of decompensation. For patients who are resistant to propranolol, other options such as endoscopic sclerotherapy, transjugular intrahepatic portosystemic shunt and shunt surgery are available[16]. It is concluded that early propranolol administration is more effective for preventing variceal bleeding in cirrhotic children and that β-blocker therapy started before esophagogastric variceal bleeding would give better results.

REFERENCES

1. Garcia-Pagán JC, Bosch J. Pharmacological prevention of variceal bleeding. New developments. Baillière's Clin Gastroenterol 1997; 11: 271-287.
2. Lebrec D, Poynard T, Hillon P, Benhamou JP. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis. N Engl J Med 1981; 305: 1371-1374.
3. Burroughs AK, Jenkins WJ, Sherlock S, et al. Controlled trial of propranolol for the prevention of recurrent variceal hemorrhage in patients with cirrhosis. N Engl J Med 1983; 309: 1539-1541.
4. Özsoylu S, Koçak N, Yüce A. Propranolol therapy for portal hypertension in children. J Pediatr 1985; 106: 317-321.
5. ConnHO, Grace ND, Bosch J, et al. Propranolol in the prevention of the first hemorrhage from esophagogastric varices: a multicenter, randomised clinical trial. Hepatology 1991; 13: 902-912.
6. The Italian Multicenter Projector for Propranolol in Prevention of Bleeding. Propranolol for prophylaxis of bleeding in cirrhotic patients with large varices: a multicenter, randomised clinical trial. Hepatology 1988; 8: 1-5.
7. Pascal JP, Cales P, Multicenter Study Grop. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. N Engl J Med 1987; 317: 856-861.
8. Villeneuve JP, Pomier-Layrargues G, Infante-Rivard C, et al. Propranolol for the prevention of recurrent variceal hemorrhage. a controlled trial. Hepatology 1986; 6: 1239-1243.
9. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-649.
10. Garcia-Tsao G, Grace ND, Groszmann RJ, et al. Short-term effects of propranolol on portal venous pressure. Hepatology 1986; 6: 101-106.
11. Feu F, Garcia-Pagán JC, Bosch J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal hemorrhage in patients with cirrhosis. Lancet 1995; 346: 1056-1059.
12. Poynard T, Glase P, Pasta L, et al. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices: an analysis of data and prognostic factors in 589 patients from four randomized clinical trials. N Engl J Med 1991; 324: 1532-1538.
13. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a metaanalytic review. Hepatology 1995; 22: 332-354.
14. Lin HC, Soubrane O, Cailmail S, Lebrec D. Early chronic administration of propranolol reduces the severity of portal hypertension and portal-systemic shunts in conscious portal vein stenosed rats. J Hepatol 1991; 13: 213-219.
15. Escorsell À, Ferayorni L, Bosch J, et al. The portal pressure response to â-blockade is greater in cirrhotic patients without varices than in those with varices. Gastroenterology 1997; 112: 2012-2016.
16. Alvarez F. Long-term treatment fo bleeding caused by portal hypertension in children. J Pediatr 1997; 131: 798-800.

Interferon - alpha treatment for chronic hepatitis C in children

Aysel Yüce[1], Nurten Koçak[1], Figen Gürakan[1], Hasan Özen[1]

[1]Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Yüce A, Koçak N, Gürakan F, Özen H. Interferon-alpha treatment for chronic hepatitis C in children. Turk J Pediatr 2000; 42: 34-38.

Interferon-alpha therapy has been proven efficient in chronic hepatitis C infection. Although it has been used as a standard therapy in adults, there are limited data on benefits of interferon treatment in children.

We conducted a study of recombinant interferon-alpha therapy in 10 children with chronic hepatitis C. They had high aminotransferase values and positive antibodies to hepatitis C virus and HCV-RNA for at leas six months. Interferon-alpha was given at a dosage of 5 million units/m^2 body surface three times a week for six months. At the end of therapy, five (50%) of the patients had complete response and two partial response. Three patients were nonresponders. Eight of the patients could be followed up for six months after stopping therapy, at which point one of the four complete responders and a partial responder relapsed. One of the three nonresponders had complete response at 12 months. Eventually, four (50%) of eight patients were complete responders. All of the nonresponders were the patients with previous malignant diseases.

These findings suggest that interferon-alpha has beneficial effects in children with chronic hepatitis C, and a six month therapy seems to be reasonable. Patients with underlying malignant disease are not good candidates for interferon treatment.

Key words: interferon, chronic hepatitis C, children.

Chronic hepatitis C is typically an insidous and slowly progressive disease. In some patients, cirrhosis and even hepatocellular carcinoma develop. It affects all age groups, but is uncomon in children[1-4]. Clinical studies have indicated that chronic hepatitis C has a poor propensity to spontaneous remission[5], and treatment is necessary with antiviral drugs.

Recently, interferon (IFN) -alpha has been used as the main medical treatment for patints with chronic hepatitis C and has been shown to be effective in decreasing the level of hepatocellular injury and inflammation and the risk of hepatocellular carcinoma[6,7]. Large randomized studies have reported the efficacy of IFN with 50 percent response rate, though the rate of relapse following IFN withdrawal is still high[7-14].

Reports about IFN-alpha treatment for chronic hepatitis C in children are rare. Here we report our experience with the use of IFN-alpha in 10 children with chronic hepatitis C virus infection.

Material and Methods

Ten children (7 boys, 3 girls) with chronic hepatitis C, aged between five and 16 years (median 8 years) were eligible for this study. Five had been treated for different types of malignancies (ganglioneuroma, ganglioneuroblastoma, Hodgkin's lymphoma, Burkitt's lymphoma and medulloblastoma) and one had sickle cell anemia. Patients were included if they had persistently elevated serum aminotransferase activities and positive HCV-RNA for the last six months before enrollment. Criteria for exclusion were antiviral or immunosuppressive therapy during the preceeding 12 months, leukopenia (< $3X10^9$/L), thrombocytopenia (< $100X10^9$/L), elevated serum creatinine level, other causes of liver disease, presence of HBsAg in serum, clinical and biochemical evidence of autoimmunity and decompensated liver disease.

Liver disease caused by alpha-1-antitrypsin deficiency and Wilson's disease was ruled out by the usual diagnostic means. At entry, patients were tested for antinuclear antibody, anti-smooth muscle antibody, anti-DNA thyroid functions, and cryoglobulinemia.

Serum samples were tested for qualitative detection of antibody to hepatitis C virus (anti-HCV) by a microparticle enzyme immunoassay

(MEIA) test (Abbott-AxSYM, HCV Version 3, USA). The kits were based on four viral antigens (HCr 43, c200, c100, NS5). HCV-RNA was copied into cDNA by reverse transcription and amplified by the nested polymerase chain reaction (PCR) using primers for the 5'-non-coding region of HCV at entry and at three-month intervals. Genotypes of HCV-RNA were determined using restriction fragment length polymorphism of the PCR product generated from the 5'-untranslated end of the genome, and genotypes were classified according to the nomenclature proposed by Simmonds et al.[15]. Liver biopsy was performed on all patients within six months before start of IFN-alpha therapy. Family members were screened for the presence of anti-HCV in serum.

Interferon-alpha treatment was initiated no sooner than three years after treatment of the underlying disease had been completed in those patients with malignancy. A written informed consent was obtained from the parents.

After evaluation, patients were started on IFN-alpha 2b (Intron-A, Schering-Plough CO. Country Cork, Ireland) subcutaneously at a dose of 5 million units/m^2 three times per week for six months. Eight patients were followed for six months after the end of treatment. Two had just finished the therapy.

Patients were evaluated monthly with liver function tests and hematological parameters during the treatment and then at three-month intervals for the following six months. An abnormal serum alanine aminotransferase (ALT) value was defined as 50 IU/L or greater.

A complete response was defined as serum ALT within normal ranges, and undetectable HCV-RNA at the end of therapy. Partial response was identified as normal ALT values or undetectable HCV-RNA. Nonresponders were those with persistently high ALT levels and positive HCV-RNA. Relapse was defined as recurrence of elevated ALT with reappearance of HCV-RNA in serum during the follow-up period.

Results

The study group consisted of 10 patients with a mean duration of hepatitis C of 11 months (range, 6-24 months). The source of hepatitis was presumed to be from blood transfusions in six and unknown in four patients. None of the family members had anti-HCV in the serum. All children were symptom free and none had a history of acute or chronic liver disease. Patients with previous malignancies had been off chemotherapy for three to 12 years (median 5 years). All had normal physical findings; serum ALT levels fluctuated between 65 and 401 IU/L. There was no evidence of autoimmunity, cryoglobulinemia or thyroid disorders in any patient.

Table I summarizes the clinical and laboratory data. Anti-HCV and HCV-RNA were positive in the serum of all 10 patients before treatment. HCV genotyping studies showed that seven patients had HCV genotype Ib, and three had genotype Ia. Liver biopsy revealed chronic persistent hepatitis in seven and mild hepatitis in the remaining three patients.

Table I. Laboratory Data in Patients Treated with Interferon-alfa 2b During Therapy and Through the Follow-up Period

		ALT (IU/L)				HCV-RNA		
Patient	Genotype	at Entry	3 mo	6 mo*	12 mo	3 mo	6 mo*	12 mo
1	Ia	65	53	12	18	+	–	–
2	Ib	231	70	40	30	–	–	–
3	Ib	175	15	15	25	+	–	–
4	Ia	151	45	17	73	+	–	+
5	Ib	89	39	34	NI	+	–	NI
6	Ia	247	130	88	68	–	–	+
7	Ib	198	70	71	NI	+	–	NI
8	Ib	85	75	69	82	+	+	+
9	Ib	197	85	69	31	+	+	–
10	Ib	232	85	86	85	+	+	+

ALT: Alanine aminotransferase (normal < 50 IU/L).
NI : Not identified.
* : End of treatment.

At the end of six months of IFN-alpha therapy, HCV-RNA became undetectable in seven patients (70%), and five of these had normal serum ALT levels. Therefore, five (50%) of the patients had complete response with normal ALT and undetectable HCV-RNA. Two were partial responders with high serum ALT and negative HCV-RNA. Three children were nonresponders. all three nonresponders and one partial responder were patients with previous malignant diseases. At the third month of treatment only two children had negative HCV-RNA Eight patients (4 complete and 1 partial responder, 3 nonresponders) were followed for six months after the end of treatment. One of the patients with complete response relapsed (patient 4); six months later HCV-RNA was detected and ALT values increased. One of the three nonresponders (patient 9) eventually cleared the virus and became a complete

responder with negative HCV-RNA and normal ALT at 12 months. The patient showing partial response became HCV-RNA positive six months after stopping the treatment. Thus, at 12 months, four of eight patients (50%) had complete response. Two nonresponders never cleared HCV-RNA and had persistently abnormal ALT. All four nonresponders were patients with underlying malignant diseae. Two nonresponders had genotype Ib and two had Ia; three respondes had HCV genotype Ib.

Every child had fever and malaise after the first doses of IFN-alpha, but no serious side effects were observed.

Discussion

The natural history and treatment of chronic hepatitis C has not been well documented in children. It seems that the disease in children usually follows an asymptomatic course and that severe liver disease is uncommon during childhood, presumably because of the slow rate of progression[10,16]. More severe disease may be expected with increasing age, and spontaneous resolution of HCV is rare. Fujisawa et al.[5] reported spontaneous remission in only 8.3 percent of children with chronic hepatitis C. Thus the treatment of chronic hepatitis C in children should be considered.

The most common modes of HCV transmission are blood transfusion and vertical transmission from mothers infected by HCV[1]. Five patients with different types of malignant diseases and one with sickle cell anemia had histories of blood transfusion. None of the mothers or other family members had anti-HCV in their sera. Thus, four of the patients (40%) had unknown etiology of HCV infection. Approximately 35-50 percent of patients with anti-HCV have been reported to have none of the risk factors for HCV infection[17,18]. Because children with malignant diseases may be immunocompromised because of the primary disease itself or of the cytotoxic agents used for treatment, IFN therapy was started at least three years after the end of treatment of primary disease.

In general, younger age, short duration of the disease, absence of cirrhosis, and mild histology have been considered as positive predictive factors for IFN treatment of chronic hepatitis C[19,20]. None of our patients had cirrhosis on the histological examinatilon, predicting response to IFN treatment. Genotype viral load also predicts the results of IFN therapy[21]. Children are at a prolonged risk for sequelae, such as cirrhosis and hepatocellular carcinoma. As they have most of the positive predictive factors naturally, children with chronic hepatitis C seem to be ideal candidates for IFN treatment. The goal of treatment in children should be to clear the virus and prevent progression to severe liver diseases. In addition to its ability to prevent the progression of liver disease, IFN is also of benefit in patients with hepatitis C virus infection who respond to this treatment, by lowering their risk of developing hepatocellular carcinoma[7,22].

In adults, IFN-alpha has been shown to induce sustained biochemical and virological response with amelioration of histological findings[23]. Little information is available about IFN treatment in children[9,14]. Complete response rate has been reported as 33-56 percent in these studies, depending on the definition of response and duration of treatment. Geographic differences may be important in response to IFN treatment, possibily due to viral genotype or host factors. In our study, 50 percent of patients had complete response at the end of six months of IFN-alpha treatment. Although two of the patients had just finished the therapy, complete response rate was the same at 12 months. An interesting point was that one child, who was a nonresponder at the end of therapy, became a complete responder at 12 months without additional therapy, similar to the report of Jonas et al.[14]. This finding may be due to spontaneous clearance of HCV. In fact, termination of IFN therapy, has been suggested for patients with positive HCV-RNA at three months of therapy[14,23]. In our study, only two of the five complete responders had negative HCV-RNA at three months of therapy. Two of seven patients (28.5%) with undetectable HCV-RNA at six months relapsed at 12 months. Jonas et al.[14] also suggested continuation of IFN treatment if the patients showed complete response at six months in order to decrease the relapse rate. Complete response rate was 33.8 percent with 12 months of therapy in their study. Although our patients were treated for only six months, complete response rate was almost similar to that in adults (50%), and the relapse rate was lower. In fact, our follow-up period was not adequate to ensure that the patients will not have a later relapse. All nonresponders at 12 months were the patients with malignant diseases. Cesaro et al.[24]

had also indicated that patients cured of a pediatric malignancy are not good candidates for IFN therapy for hepatitis C.

Recent investigators have shown that the HIV genotype was one of the important factors in predicting response to IFN therapy[19]. In most series, genotype Ib has been shown to be associated with higher HCV-RNA levels, more severe hepatitis, and a higher frequency of decompensated cirrhosis, and patients infected with HIV genotype Ia or Ib show poor response to IFN treatment[9,19,25,26]. Although seven of our patients had HCV genotype Ib and three had genotype Ia, complete response rate of IFN treatment in our patients was higher than that in these studies. Nonresponders had both HCV genotype Ia and Ib.

IFN has a variety of side effects, some of which cause dose decrease or discontinuation of the therapy. In this study, IFN-alpha was generally well tolerated, and only an influenza-like syndrome was seen during the first doses of IFN.

This study showed that IFN-alpha was safe and had beneficial effects in children with chronic hepatitis C, but it is not hopeful in patients with underlying malignant disease. A combination of ribavirin and IFN may be effective in cases unresponsive to IFN therapy[27]. Ongoing HCV-RNA positivity at the third month did not imply nonresponse in our three patients. As termination of therapy for nonresponders at the third month does not seem to be reasonable, we suggest at least six months of therapy, even if HCV-RNA persists at the third month. In fact, further long-term studies with larger numbers of patients are needed to show the real efficacy of IFN treatment in children with chronic hepatitis C.

Acknowledgement

The authors thank Dr. Mithat Bozdayı, Ankara University, Department of Gastroenterology, for performing viral genotyping for this study.

REFERENCES

1. Bortolotti F, rosti M, Giacchino R, et al. Changing epidemiologic pattern of chronic hepatitis C virus infection in Italian children. J Pediatr 1998; 133: 378-381.
2. Bellantani S, Tiribelli C, Saccoccio G, et al. Prevalence of chronic liver disease in the general population of northern Italy: the dionysus study. Hepatology 1994; 20: 1442-1449.
3. Yüce A, Koçak N, Özen H, Gürakan F. Low prevalence of antibody to hepatitis Cc virus in children with chronic liver disease. Eur J Pediatr 1997; 156: 153.
4. Özen H, Koçak N, Yüce A, Gürakan F. Low prevalence of hepatitis C virus antibody in Turkish children with chronic hepatitis B infection. J Hepatol 1995; 23: 480.
5. Fujesawa T, Komatsu h, Inui A, et al. Spontaneous remission of chronic hepatitis C in children. Eur J Pediatr 1997; 156: 773-776.
6. Iorio R, Pensati P, Porzio J, Fariello I, Guida S, Vegnente A. Lymphoblastoid interferon alfa treatment in chronic hepatitis C. Arch Dis Child 1996; 74: 152-156.
7. Serfaty L, Aumaitre H, Chazouilléres O, et al. Determinations of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998; 27: 1435-1440.
8. Di Bisceglie AM, Martin P, Kassianider C, et al. Recombinant interferon alpha therapy for chronic hepatitis C. A randomized double blind, placebo controlled trial. N Engl J Med 1989; 321: 1506-1513.
9. Davis GL, Balart LA, Schiff E, et al. Treatment of chronic hepatitis C with recombinant interferon alfa. N Engl J Med 1989; 321. 1501-1506.
10. Bortolotti F, Giacchino R, Vajro P, et al. Recombinant interferon-alpha therapy in children with chronic hepatitis C. Hepatology 1995; 22: 1623-1627.
11. 10. Fujisawa T, Inui A, Okhawa T, Komatsu H, Miyakawa Y, Onoue M. Response to interferon therapy in children with chronic hepatitis C. J pediatr 1995; 127: 660-662.
12. Ruiz-Moreno M, Rua MJ, Castillo I, et al. Treatment of children with chronic hepatitis C with recombinant interferon-alfa: a pilot study. Hepatology 1992; 16: 882-885.
13. Matsuoka S, Mori K, Nakano O, et al. Efficacy of interferons in treating children with chronic hepatitis C. Eur J Pediatr 1997; 156: 704-708.
14. Jonas MM, Ott JJ, Nelson SB, Badizadegan K, Perz-Atayde AR. Interferon-alpha treatment of chronic hepatitis C virus infection in children. Pediatr Infect Dis J 1998; 17: 241-246.
15. Simmonds P, Alberti A, Bonino F, et al. A proposed system for nomenclature of genotypes of hepatitis C virus. Hepatology 1994; 19: 1321-1324.
16. Bortolotti F, Jara P, Diaz C, Vajro P, et al. Posttransfusion and community-acquired hepatitis C in childhood. J Pediatr Gastroenterol Nutr 1994; 18: 279-283.
17. A-kader HH, Balistreri WF. Hepatitis C virus: implications to pediatric practice. Pediatr Infect Dis J 1993; 12: 853-867.
18. Zeuzem S, Tevber G, Lee JH, Ruster B, Roth WK. Risk factor for the transmission of hepatitis C. J Hepatol 1996; 24 (Suppl) 3-10.
19. Tsubota A, Chayama K, Ikeda K, et al. Factors predictive of response to interferon-alfa therapy in hepatitis C infection. Hepatology 1994; 19: 1088-1094.
20. Niederau C, Lange S, Heintges T, et al. Prognosis of chronic hepatitis C: results of a large, prospective cohort study. Hepatology 1998; 28: 1687-1695.
21. Bell H, Hellum K, Harthug S, et al. genotype, viral load and age as independent predictors of treatment outcome of interferon-α 2a treatment in patients with chronic hepatitis C. Scand J Infect Dis 1997; 29: 17-22.

22. Mazzella G, Accogli E, Sottili S, et al. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. J Hepatol 1996; 24: 141-147.

23. Sim H, Yim C, Krajden M, Heathcote J. Durability of serological remission in chronic hepatitis C treated with interferon-alpa-2B. Am J Gastroenterol 1998; 93: 39-43.

24. Cesaro S, Rozzetti f, de Moliner L, Crivellaro C, Zanesco L, Bortolotti F. Interferon for chronic hepatitis C in patients cured of malignancy. Eur J Pediatr 1994; 153: 659-662.

25. Yoshioka K, higashi Y, Yamada M, et al. Predictive factors in the response to interferon therapy in chronic hepatitis C. Liver 1995; 15: 57-62.

26. Nousbaum JB, Pol S, Nalpas P, et al. Hepatitis C virus type Ib (II) infection in France and Italy. Ann Intern Med 1995; 122: 161-168.

27. reichard O, Norkrans G, Frydén A, Braconier J-H, Sönnerborg A, Weiland O. Randomised, double-blind, placebo-controlled trial of interferon α-2b with and without ribavirin for chronic hepatitis C. Lancet 1998; 351: 83-87.

Bacterial nosocomial infections in mechanically ventilated children

Agop Çıtak[1], Metin Karaböcüoğlu[1], Raif Üçsel[1], Serpil Uğur-Baysal[1], Nedret Uzel[1]
[1]Department of Pediatric Emergency, İstanbul University Institute of Child Health, İstanbul, Turkey

SUMMARY:. Çıtak A, Karaböcüoğlu M, Üçsel R, Uğur-Baysal S, Uzel N. Bacterial nosocomial infections in mechanically ventilated children. Turk J Pediatr 2000; 42; 39-42.

Of 480 patients admitted to the Pediatric Intensive Care Unit of the Institute of Child Health Children's Hospital in İstanbul, 97 required mechanical ventilation (MV). Sixty of these children were included in a retrospective analysis aiming to determine the frequency of and factors contributing to the development of nosocomial infections (NI). NI rate was 45 percent, ventilator-associated pneumonia (VAP) accounted for the greater part (66.7%) of the NI, followed by urinary tract infections (16.7%), septicemia (13.3%), and meningitis (3.3). Pseudomonas aeruginosa was the most frequent cause of VAP. The duration of the MV and invasive interventions were important risk factors for the development of VAP.

Key words: nosocomial infections, mechanical ventilation pediatric intensive care unit, ventilator-associated pneumonia.

Nosocomial infections (NI) are a major health problem due to the excessive morbidity, mortality and need for prolonged hospitalization. A significant portion (25%) of all NI occur in intensive care units[1-4]. Pneumonia ranks second in frequency among hospital-acquired infections, and patients in Pediatric Intensive Care Units (PICU) have a higher incidence of nosocomial pneumonia than other pediatric hospital patients. Peumonia is also the most common fatal nosocomial infection in PICU. Depending on the causative organism and the primary illness, mortality rates ranging from 20 to 70 percent are reported in PICU patients with pneumonia[1,4]. Causative organisms are often antibiotic resistant[1-3].

The severity of the primary condition and exposure to life-saving invasive procedures are closely associated with the development of NI. Other related factors are the length of stay in intensive care and the use of antibiotic therapy that may alter the patient's flora[4-6]. Age is another important factor, with patients in the youngest and oldest age brackets having the highest infection rates[5,7-9].

In this retrospective analysis, we aimed to evaluate the incidence of NI and the risk factors leading to NI in the PICU of a university hospital in İstanbul. Our experience with nosocomial pneumonia in critically ill patients requiring mechanical ventilation will also be presented.

Material and Methods

This study was conducted by analyzing the files of patients admitted to the PICU of the Institute of Child Health in İstanbul during a one year period from January 1 to December 30, 1996. This Unit functions with a capacity of four beds and admits around 400 patients yearly.

All patients who required mechanical ventilation (MV), with the exception of newborn babies and patients who stayed in the Unit for a period shorter than 48 hours, were included in the analysis. data on age, sex, length of MV, other invasive procedures used (central venous catheters, bladder catheterization), nutrition (parenteral, enteral), and the use of H_2-receptor antagonists were collected retrospectively from patient charts. The microbial cultures of infections were also reviewed.

Criteria for dignosis of nosocomial infection were based on clinical (fever higher than 38 °C, systemic symptoms) and laboratory (a peripheral leukocyte count greater than 10,000 per mm^3 and presence of microorganisms in cultures) findings. A diagnosis of pneumonia was made when, in addition to clinical and laboratory evidence of infection, auscultatory findings were indicative of pneumonia, and/or when pulmonary infiltrates appeared on the chest radiograph. A nosocomial infection was considered ventilator-associated

when its onset occurred after a minimum period of 48 hours following the initiation of mechanical ventilation[9-11]. In the patients who were in mechanical ventilation due to infectious disease, a nosocomial infection was considered when these conditions appeared: recurrence of fever, requisite changing of mechanical ventilation parameters, increase of a peripheral leukocyte count greater than 10,000 per mm^3, alterations in chest radiograph and detection of microorganism in cultures. If there was no evidence of an infection with clinical, radiological and laboratory findings, the microbiological agents detected in the endotracheal aspirate cultures were regarded as colonization[9-11].

The data of patients who developed NI were compared with data from those who did not, using Student's t-test or comparison of proportions.

Results

During the 12-month period a total of 480 patients were admitted to PICU and 97 patients required MV. Sixty of these 97 patients conformed to the criteria described above and were included in the study; 27 (45%) of these patients developed NI. The pertinent features of the patients are shown in Table I. All patients were directly referred to the Intensive Care Unit upon arrival to hospital. In 80 percent of the patients, an endotracheal tube was in the first 24 hours and mechanical ventilation was initiated. In the remaining 20 percent, endotracheal tubes were administered in the first 48 hours. Patients who developed NI and those who did not were similar in age and sex, but there were statistically significant differences between the two groups with regard to duration of MV and use of central venous catheter, of total parenteral nutrition and of H_2-receptor antagonists.

Ventilator-associated pneumonia (VAP) was the most common NI (66.7%) in mechanically ventilated patients. Urinary tract infeactions (16.7%), septicemia (13.3%) and meningitis (3.3%) were the other nosocomial infections (Fig. 1):

Table I. Characteristics of the Study Population

	NI absent	NI present	p
Number of patients	33	27	
Female/Male ratio	1.03	1.07	
Age (decimal years)			
Mean	0.83±1.38	1.49±2.20	p=0.74
Range	33 days-12 years	2 months-11 year	
Duration of MV (days)			
Mean	3.6±1.5	15.1±16.7	p<0.001
Range	2-8	3-90	
Interventions			
Central venous catheter	0	22%	p=0.0001
Urinary catheter	96%	100%	p=0.249
Parenteral nutrition	6%	56%	p=0.002
H_2 blocker	57.6%	89%	p=0.016
Mortality	27% (9)	26% (7)	p=0.836

NI: nosocomial infections; MV: mechanical ventilation.

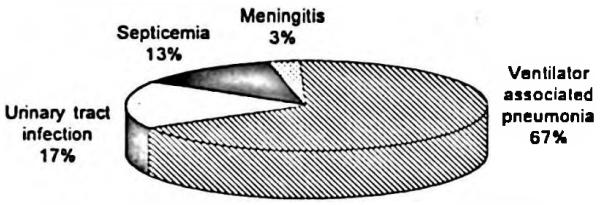


Fig. 1. The distribution of nosocomial infections.

Primary diseases in patients with and without NI are shown in Table II. mortality rate was 26 percent in the NI group and 27 percent in the group free of nosocomial infections ($p > 0.05$).

Table II. Primary Disease in Patients with and without NI

Disease	NI absent (n)	NI present (n)
Sepsis	14	11
Bronchopneumonia	4	3
Bronchiolitis	2	2
Congenital heart disease	2	–
Meningitis		1
Bacterial	2	–
Viral	1	–
Tuberculosis	1	1
Encephalitis	3	2
Meningococcemia	2	–
Myocarditis	1	–
Carbon monoxide poisoning	1	–
Status epilepticus	–	4
Guillain-Barré syndrome	–	1
Hemolytic uremic syndrome	–	1
Congenital metabolic disorders	–	2
Total	33	28

NI: nosocomial infections.

Pseudomonas aeruginosa was the most frequent cause of nosocomial pneumonia (Table III). Candida albicans was the most frequent cause of the urinary infections. Methicillin-resistant Staphylococcus aureus (MRSA) and Klebsiella pneumoniae were frequent causes of septicemia.

The vast majority of patients presenting to our institution primarily with an infectious disease had already received oral or parenteral antibiotics and their cultures remained sterile.

Discussion

Sepsis was the most common primary clinical diagnosis in patients admitted to our PICU. The frequency of sepsis as a primary diagnosis was similar in the NI group (42%) and in patients free of NI (40%). This finding may reflect the

Table III. Microorganisms Identified and Culture Source

Endotracheal tubes n. 25	Urine n: 5	Blood n: 4	Cerebrospinal fluid n: 1
P. aeruginos (8)	Candida albicans (3)	Methicillin-resistant staphylococcus (2)	Methicillin-resistant staphylococcus (1)
Methicillin-sensitive staphylococcus (4)	E. coli (1)	Klebsiella (1) pneumoniae	
Methicilin-resistant staphylococcus (3)	Klebsiella pneumoniae (1)	Other Gram-negative organisms (1)	
Klebsiella pneumoniae (2)			
Acinetobacter (1)			
Enterobacter (1)			
Klebsiella oxytoca (1)			
α-hemolytic streptococci (1)			
Stenotrophomonas maltophilia (1)			
H. influenza (1)			
other Gram-negative organisms (2)			

high frequency of infections as a cause for hospitalization in the Turkish pediatric population. Indeed, infections comprise 30 percent of total admission to the University Children's Hospital of İstanbul. On the other hand, bacteria were demonstrated in only 13 percent of our patients with NI. This lower frequency may be due to the low positive culture ratios obtained in our hospital laboratory.

Haley et al.[12] found that the pneumonia frequency in MV patients was 21 times greater than in non-ventilated patients. In our patients we also found pneumonia related to ventilation to be the most frequent NI. Multiple factors play a role in the pathogenesis of ventilation-related pneumonia, but two of these, namely, aspiration of highly colonized oropharyngeal secretions and inhalation of contaminated aerosol, have been to be of special significance[10,13,14]. The severity of the disease, duration of hospitalization in the intensive care unit, age of the patient, antibiotic therapy, endotracheal intubation, tracheostomy, H2 receptor blockers and/or antacids, malnutrition, presence of any lung disease, uremia, gastric colonization, hand disinfection of the patient and of the medical personnel and nasogastric tubing are all major factors causing a high colonization in the oropharynx[13,15,16]. A positive correlation can also be found between the duration of MV and ventilator-related pneumonia frequency[13,15,16,18]. Fagon et al.[18] found that ventilator-related pneumonia risks increased by one percent for each day the patient stayed on the ventilator. In our study, we also showed that nosocomial infections, especially ventilator-associated pneumonia, were significantly related to the duration of MV, with the NI rate increasing with longer duration (Table I). Use of central venous catheters and total parenteral nutrition were additional risk factors.

Gram-negative bacteria, usually of gastrointestinal source, are reported as the main agents causing pneumonia[12-14]. When examined from this aspect, there is a relationship between gastric colonization and oropharyngeal colonization. In our study, the most frequent agent in ventilator-associated pneumonia was the Pseudomonas species and the second most frequent was staphylococcus.

As gastric pH is decreased in patients on H2-receptor antagonists, Gram-negative bacilli can easily be colonized in the gastrointestinal tract. It has been shown that ventilator-related pneumonia probability is twice as high in H2-receptor blocker and/or antacid-using patients[1,10,11]. In our study, the H2-receptor blocker prescription rate was significantly greater in the patients who developed ventilator-associated pneumonia.

Bacterial nosocomial infections, especially nosocomial pneumonia, acquired in the intensive care unit are a major cause of morbidity and mortality[1,17,18]. In our study, the mortality rate in the NI group was not statistically different from that in the NI-free group. It is difficult to interpret this unexpected result which may be related to the small number of patients.

Ventilator-related pneumonia is seen more frequently in winter and autumn months. Viral and mycoplasma infections are thought to play

an important role in this[1,6]. However, there is insufficient data to justify a necessity for routine cultures for these microorganisms.

In conclusion, our data support previous findings and indicate that a high frequency of NI, especially of ventilator-associated pneumonia, is encountered in MV patients, with the duration of MV and use of invasive procedures begin major risk factors in the development of NI. The data also show that Gram-negative bacteria continue to occupy first rank in NI among pediatric patients in a developing country setting.

Acknowledgements

Authors are indebted to Prof. Dr. Olcay Neyzi for her critical review of this manuscript.

REFERENCES

1. Stein F, Trevino R. Nosocomial infections in the pediatric intensive care unit. Pediatr Clin North Am 1994; 41: 1245-1255.
2. Preston GA, Larson EL, Stamm WE. The effect of private isolation rooms on patient care practices, colonization and infection in an intensive care unit. Am J Med 1981; 70: 641-645.
3. Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. Am Rev Respir Dis 1986; 133: 792-796.
4. Özsüt H. Nosocomial Infections in Intensive Care Units. İstanbul: Office Print; 1997: 54.
5. Çakar N, Tütüncü A. The hospitalisation in intensive care unit, invasive procedures and the problem of infections. Klimig Derg 1996; 9: 3-5.
6. Merritt WT, Green M. Nosocomial infections in the pediatric intensive care unit. In. Rogers MC (ed). Textbook of Pediatric Intensive Care. Philadelphia: Williams&Wilkins; 1996: 975-1010.
7. Rouby JJ, Lassale EM, Poete P, et al. Nosocomial bronchopneumonia in the critically ill. Am Rev Respir Dis 1992; 146: 1059-1066.
8. Chastre J, Fagon JY, Trouillet JL. Diagnosis and treatment of nosocomial pneumonia in patients in intensive care units. Clin Inf Dis 1995; 21 (Suppl): 226-237.
9. Celis R, Torres A, Gatell JM, Almella M, Roisin RR, Vidal AA. Nosocomial pneumonia. Chest 1988; 92: 318-324.
10. Torres A, Aznar R, Gatell JM, et al. Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. Am Rev Respir Dis 1990; 142: 523-528.
11. Rello J, Torres A, Ricart M, et al. Ventilator-associated pneumonia by Staphyloccus aureus. Am Respir Crit Care Med 1994; 150: 1545-1549.
12. Meta-analysis of randomised controlled trials of Selective Decontamination of the Digestive Tract Trialists Collaborative Group. Br Med J 1993; 28: 525-532.
13. Hammond JM, Potgieter PD, Saunders GL, Forder AA. Double-blind study of selective decontamination of digestive tract in intensive care. Lancet 1992; 340: 5-9.
14. A'Court C, Garrard CS. 1-Nosocomial pneumonia in the intensive care unit: mechanism and significance. Thorax 1992; 47: 465-473.
15. Bonten MJ, Bergmans DC, Ambergen AW, et al. Risk factors for pneumonia, and colonization of respiratory tract and stomach in mechanically ventilated ICU patients. Am Respir Crit Care Med 1996; 154: 1339-1346.
16. Winfield JA, Rosenthal P, Kanter RK, Casella G. Duration of intracranial pressure monitoring does not predict daily risk of infectious complications. Neurosurgery 1993; 33: 424-431.
17. Craven DE, kunches LM, Lichtenberg DA, et al. Nosocomial infections and fatality in medical and surgical intensive care unit patients. Arch Intern Med 1988; 148: 1161-1168.
18. Fagon JY, Chastre J, Hance AJ, et al. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 1993; 94: 281-288.

Balloon dilatation angioplasty of stenosed systemic - pulmonary artery shunts

İrfan Levent Saltık[1], Ayşe Güler Eroğlu[1], Funda Öztunç[1], Ayşe Sarıoğlu[1]

[1]*Department of Pediatric Cardiology, İstanbul University Institute of Cardiology, İstanbul, Turkey*

SUMMARY: Saltık İL, Eroğlu AG, Öztunç F, Sarıoğlu A. Balloon dilatation angioplasty of stenosed systemic-pulmonary artery shunts. Turk J Pediatr 2000; 42: 43-47.

Seven children and an adult patient with cyanotic congenital heart defects underwent balloon dilatation angioplasty (BDA) of a stenosed systemic-pulmonary artery shunt to improve arterial oxygen saturation. We attempted to perform BDA using the transvenous route in all patients in whom the aorta connected with the right ventricle, such as in tetralogy of Fallot or double outlet right ventricle, in an effort to avoid femoral artery injury. We could use the transvenous route (antegrade) in three children with tetralogy of Fallot and in one child with tetralogy of Fallot and pulmonary atresia (one of them was 6.6 kg). Fallowing BDA, there was an increase in arterial oxygen saturation from a mean of 65.9 ± 12.8% to a mean of 78.1 ± 8.3% ($p < 0.05$). On follow-up three to 37 months (mean 16.5 ± 11.2 months) after BDA, the condition of all patients had improved. Pulmonary hypertension developed in one patient during the follow-up period. It is concluded that BDA of stenosed systemic-pulmonary artery shunts is reasonable, effective and safe. Use of the transvenous route, if possible, to perform balloon dilatation angioplasty facilitates the safe advancement of the larger balloons in low-weight children.

Key words: balloon dilatation angioplasty, systemic-pulmonary artery shunts, Blalock-Taussig shunts.

Systemic-pulmonary artery shunts are standard palliative treatment for various cyanotic congenital heart defects with reduced pulmonary blood flow. Early or late occlusion of systemic-pulmonary artery shunts occurs in approximately 10 percent of cases[1,2]. Recently, balloon dilatation angioplasty (BDA) of stenosed systemic-pulmonary artery shunts has been used successfully in pediatric patients who were not amenable for surgical correction and in those in whom the correction needed to be delayed, in order to avoid the morbidity and potential mortality of a new systemic-pulmonary artery shunt operation. BDA, performed in a retrograde manner through the femoral artery, has been well described in the literature[3-8]. We attempted to perform the procedure using the transvenous route in all patients in whom the aorta connected with the right ventricle, such as in tetralogy of Fallot or double outlet right ventricle, to avoid femoral artery injury and to safely advence the larger balloons.

In this report, we review our experience with balloon dilatation angioplasty of stenosed systemic-pulmonary artery shunts and illustrate the usefulness of using the transvenous route, if possible.

Material and Methods

Study Patients: From November 1994 to November 1996, seven children aged 1 to 11.6 years (mean 4.3 ± 3.7 years) and one adult aged 38 years underwent BDA of stenosed systemic-pulmonary artery shunts to improve arterial oxygen saturation. After clinical assessment and the usual laboratory studies suggestedd hypoxemia and pulmonary oligemia in association with a cyanotic heart defect, cardiac catheterization was performed both to confirm the clinical diagnosis and to prepare for possible balloon dilatation angioplasty, (Figs. 1a, 1b, 1c).

Technique: We attempted to use the transvenous route (antegrade) in five patients and could pass

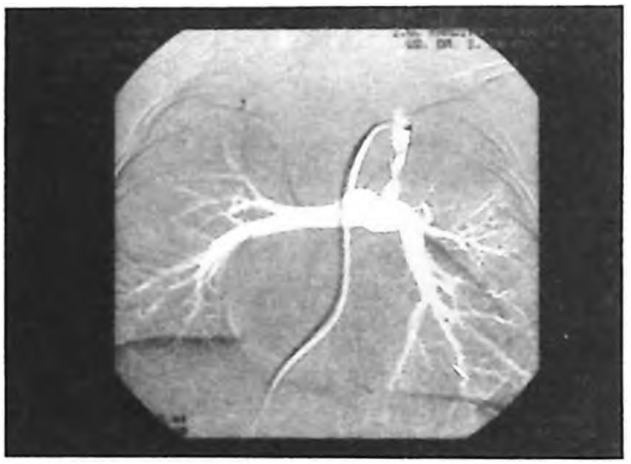


Fig. 1a. Digital subtraction angiography of left modified Blalok-Taussig shunt demonstrates marked narrowing of the shunt (transvenous route).

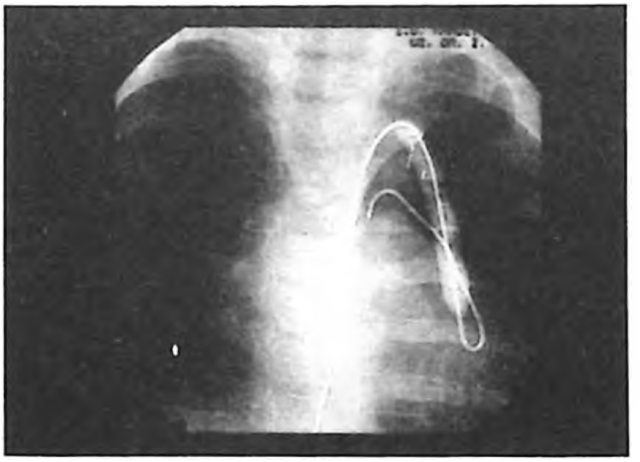


Fig. 1b. Position of balloon dilatation catheter during inflation.

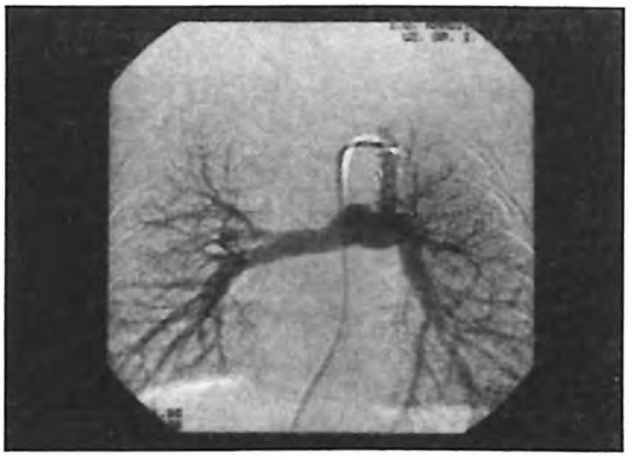


Fig. 1c. Digital subtraction angiography of left modified Blalock-Taussig shunt demonstrates relief of stenosis of the shunt and improvement in pulmonary flow.

a catheter into the aorta through the femoral vein in four of them (Cases 2, 3, 6, 8). We used arterial routes (retrograde) in four patients (Cases 1, 4, 5, and 7). In each case 50 units/kg of heparin (maximum 2500 units) were administered immediately after introduction of the sheath. A 6F right coronary artery catheter in Cases 2, 6, and 8 and a 6F LIMA catheter in Case 3 was placed in the right ventricle by femoral venous route. The tip of the catheter was positioned in the mouth of the aorta via the ventricular septal defect. A floppy guide wire was advanced through the catheter and positioned within the aorta with suitable guidewire manipulation. The catheter was advanced over the floppy guidewire into the aorta and then placed at the origin of the systemic-pulmonary artery shunts. A 6F right coronary artery catheter or a 6F LIMA catheter, and in one case a 4F multipurpose catheter, was passed retrogradely through the femoral artery and placed at the origin of the systemic-pulmonary artery shunts. After pressure and saturation measurements, shunt angiography was performed in all patients to confirm the site and the severity of the stenosis and to measure the diameter of the shunt. A floppy guidewire or hydrophilic wire (Terumo) could be passed across the stenosed systemic-pulmonary artery shunt in all patients and the catheter placed in the pulmonary artery over the guidewire.

A 260 cm long 0.032 inch exchange guidewire in seven patients and a standard coronary guidewire in Case 7 was advanced through the catheter and positioned distally within the pulmonary artery. The catheter was removed and a balloon dilatation catheter (meditech) with appropriate balloon diameter was then inserted over the exchange

guidewire and advanced into the systemic-pulmonary artery shunt so that the midsection of the balloon was at he point of stenosis. The balloon was inflated until the balloon waist disappeared, to a maximum of 10 atmospheric pressure. After the procedure, saturation, pressure measurements and angiography were repeated in all cases. All patients were discharged within 24 hours of the procedure.

Follow-up

Follow-up clinical studies, hematocrit and echo-Doppler studies were available in all patients after three to 37 months (mean 16.5 ± 11.2 months). Recatheterization was performed in Case 1 at 31 months, in Case 2 at 28 mnths and in Case 7 at 15 months after BDA.

Statistics

Data are expressed as mean ± SD. The Student's t test was used for comparison of data obtained prior to and following angioplasty. Statistical significance was inferred at a value of $p < 0.05$.

Results

Anthropometric characteristics, diagnoses, sites and types of the systemic-pulmonary artery shunts and other characteristics about balloon dilatation angioplasty are shown in Table I. Continuous murmur of the shunt was absent in four patients and decreased in the others. All patients were cyanotic with increased hematocrit values of mean 57 ± 8.3 percent, with a range of 48 to 68 percent. There was moderate to severe hypoxemia with a mean oxygen saturation of 65.9 ± 12.8 percent, with a range of 50 to 82 percent. In Case 5, despite high arterial oxygen saturation (82%), balloon dilatation angioplasty was performed because of severe anatomical narrowing of the shunt.

In all patients there was significant improvement. Auscultation revealed continuous murmur of the shunt. The stenosis diameter increased from 1.9 ± 0.8 mm to 4.4 ± 0.4 mm following BDA ($p < 0.05$). the arterial oxygen saturation increased from a mean of 65.9 ± 12.8 percent to, mean of 78.1 ± 8.3 percent ($p < 0.05$). Pulmonary arterial peak systolic pressure was mean 13 ± 5 mmHg before the procedure and mean 18 ± 7 mmHg, with a range of 7 mmHg to 30 mmHg, after the procedure. no complications were encountered during the procedure.

The patients were followed three months to 37 months (mean 16.5 ± 11.2 months). The patients with symptoms of exercise intolerance improved markedly, although all of them remained cyanotic. Hematocrit values decreased from mean 57 ± 8.3 percent to mean 48.8 ± 7.4 percent ($p < 0.05$). Auscultation revealed continuous murmur of the shunt and the shunts were patent on echo-Doppler study in all patients. Three patients underwent repeat cardiac catheterization. In the adult patient (Case 1) congestive heart failure developed two months after BDA and was treated with digoxin and diuretics. Left pulmonary artery pressures of 105/65 mmHg, with an aortic pressure o 125/70 mmHg, were obtained. Angiography demonstrated a widely patent subclavian to left pulmonary artery shunt. Pulmonary artery pressures were normal and shunts were patent in Case 2 28 months and in Case 7 15 months

Table I. Patient Data: Balloon Dilatation of Stenosed Systemic-Pulmonary Artery Shunts

				Shunt		Stenosis D (mm)		SAT (%)		Pa press (mmHg)		Ao press (mmHg)		Hct (%)		
Pt	Age (year)	Weight (kg)	Diagnosis	Site type	BD (mm)	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Follow-up (mos)
1	38	61	TA, PS, HPA, RGA	L BT	5,7	0.7	5.4	80	89	19	30	120	75	68	57	37
2	11.6	26	FT, PA, HPA, APT, OC, LMBT	R BT	5,6,7	0.7	4.7	73	83	7	15	95		48	40	28
3	1	6b6	FT, PA, HPA	L MBT	6	2.3	4.5	50	70	15	17	100	110	53	46	7
4	5.3	22	M, AVD, ASD, VSD, DORV, PS	L MBT	6	2.8	4.6	63	74	10	18	110	100	62	50	3
5	5.3	20	DORV, VSD, PS, ALPA	R CEN	5	1.8	4	82	89	12	20	90		60	52	11
6	4	10	FT, HPA	L MBT	6	1.8	4.4	48	68	7		100	90	65	50	18
7	0.75	8.3	AVD, DORV, VSD, PS	L MBT	5	2.6	4.9	50	62	17	20	80		44	37	15
8	2.2	10	FT, PA	R MBT	5	2.5	5	71	80	17	20	85	90	56	50	13

ALPA: absence of the left pulmonary artery, Ao press: aorta systolic pressure, APK: aortapulmonary collateral arteries, ASD: atrial septal defect, AVD: atrioventricular discordance, BD: balloon diameter, BT: Blalock-Taussig, D: diameter, DORV: double outlet right ventricle, FT: tetralogy of Fallot, Hct: hematocrit before dilatation and at the last follow-up, HPA: hypoplastic pulmonary arteries, L: left, M: mesocardia, MBT: modified Blalock-Taussig, OC: occluded, PA: pulmonary atresia, Pa press: pulmonary artery systolic pressure, PS: pulmonary stenosis, R: right, RGA: right Glenn anastomosis, SAT (%): systemic oxygen saturation before and after dilatation, TA: tricuspid atresia, VSD: ventricular septal defect, LMBT: left modified Blalock-Taussig, CEN: central.

after BDA. In case 2, the McGoon ratio was increased from 1.5 to 1.7 and total correction was performed. In other cases the McGoon ratio did not change during the follow-up period, but it was short in Case 3 and Case 4 (7 months and 3 months, respectively).

Discussion

When a systemic-pulmonary artery shunt becomes stenosed in a cyanotic congenital heart defect with reduced pulmonary blood flow, the therapeutic options include the creation of another systemic-pulmonary artery shunt or, if suitable, correction of the underlying cardiac malformation earlier than planned[1,2]. Transcatheter balloon dilatation of stenosed shunts has been proposed as an alternative to a new systemic-pulmonary artery shunt[5]. In published reports, transcatheter balloon dilatation of stenosed systemic-pulmonary artery shunts was done via the arterial route (retrograde)[3-8]. We used the transvenous route to perform coronary angiography in the patients with tetralogy of Fallot and to measure pulmonary artery pressure passing through the systemic-pulmonary artery shunt in the patients with an aorta that connects with the right ventricle, such as tetralogy of Fallot, double outlet right ventricle or transposition of great arteries, to avoid femoral artery injury. It is easier to pass through the right modified Blalock-Taussig shunt than the left modified Blalock-Taussig shunt. We could use the transvenous route in three children with tetralogy of Fallot and pulmonary atresia and in one patient with tetralogy of Fallot, (1 weighed only 6.6 kg). We used the arterial route in the adult patient with tricuspid atresia and pulmonary stenosis and in two patients with double outlet right ventricle and atrioventricular discordance in whom the systemic venous atrium was not connected with the right ventricle. We also used the arterial route in a patient with double outlet right ventricle and central shunt because of insufficient experience with passing a central shunt. There is potential risk of arrhythmia with the transvenous technique because the catheter passes through the heart. We decreased this risk using a floppy or hydrophilic guidewire to pass into the aorta via the ventricular septal defect, and our patients did not have any arrhythmia. Using the transvenous route, if possible, to perform BDA prevents femoral artery injury and permits the safe advancement of the larger balloons.

Transcatheter balloon dilatation of stenosed systemic-pulmonary artery shunts was successful, but the results depended on the size of the balloon in relation to the size of the shunt[4,6,7,9]. An oversized balloon, for example, may cause increased pulmonary blood flow leading to congestive heart failure in the short term and pulmonary hypertension in the long term[9]. In order to avoid these complications, we completed the procedure when the diameter of the anastomotic site increased to 5 mm, except in the adult patient (Case 1). In this Case, a 7 mm balloon catheter was used and stenosis diameter neached 5.7 mm after the balloon dilatation angioplasty. Pulmonary hypertension developed during follow-up. A remaining fundamental question is the magnitude of ideal dilatation. Recently, successful balloon dilatation angioplasty and stent implantation have been reported in pediatric patients with stenosed or occluded systemic-pulmonary artery shunts[10,11].

We believe that balloon dilatation angioplasty of stenosed systemic-pulmonary artery shunts is a reasonable and safe alternative to reoperation in those patients who are amenable to total surgical correction and in those in whom the correction needs to be delayed. Using the transvenous route, if possible, to perform balloon dilatation angioplasty permits the safe advancement of the larger balloons in low-weight children.

REFERENCES

1. Arciniegas E, Farooki ZQ, Hakimi M, Perry BL, Green EW. Classic shunting operations for congenital cyanotic heart defects. J Thorac Cardiovasc Surg 1982; 84: 88-96.
2. Stewart S, Alexson C, Manning J. Long-term palliation with the classic Blalock-Taussig shunt. J Thorac Cardiovasc Surg 1988; 96: 117-121.
3. Galal O, Qureshi SA. Balloon dilation recanalization of completely occluded modified Blalock-Taussig shunt. Cardiol Young 1994; 4: 178-180.
4. Marasini M, Dalmonte P, Pongiglione G, et al. Balloon dilatation of critically obstructed modified (polytetrafluoroethylene) Blalock-Taussig shunts. Am J Cardiol 1994; 15: 405-407.
5. Marx GR, Allen HD, Ovitt TW, Hanson W. Balloon dilation angioplasty of Blalock-Taussig shunts. Am J Cardiol 1988; 62: 824-827.
6. Qureshi SA, Martin RP, Dickinson DF. Balloon dilatation of stenosed Blalock-Taussig shunts. Br Heart J 1989; 61. 432-434.
7. Rao PS, Levy JM, Chopra PS. Balloon angioplasty of stenosed Blalock-Taussig anastomosis: role of balloon-on-a-wire indilating occluded shunts. Am Heart J 1990; 120. 1173-1178.

8. Sreeram N, Walsh K, Peart I. Recanalisation of an occluded modified Blalock-Taussig shunt by balloon dilatation. Br Heart J 1993; 70: 474-475.
9. Fernandes J, Kan JS. Late outcome after successful balloon dilatation of Blalock-Taussig variant shunt stenosis. Am J Cardiol 1991; 67: 1440-1444.
10. Peuster M, Fink C, Bertram H, Paul T, Hausdorf G. Transcatheter recanalization and subsequent stent implantation for the treatment of early postoperative thrombosis of modified Blalock-Taussig shunts in two children. Cathet Cardiovasc Diagn 1998; 45. 405-408.
11. Zahn EM, Chang AC, Aldousany A, Burke RP. Emergent stent placement for acute Blalock-Taussig shunt obstruction after stage 1 Norwood surgery. Cathet Cardiovasc Diagn 1997; 42: 191-194.

Regressed retinopathy of prematurity in children aged 5 - 8 years in Sivas, Turkey

Özkan Ergür[1], Ayça Törel Ergür[2], Cenap Güler[1]

[1]Department of Ophthalmology, and [2]Department of Pediatrics, Cumhuriyet University Faculty of Medicine, Sivas, Turkey

SUMMARY: Ergür Ö, Törel Ergür A, Güler C. Regressed retinopathy of prematurity in children aged 5-8 years in Sivas, Turkey. Turk J Pediatr 2000; 42: 48-52.

In this present study regressed retinopathy of prematurity has been investigated in children born prematurely (< 2300 g birth weight and < 34 weeks gestational age) in Sivas, Turkey during January 1989-January 1992. At the age of 5-8 years, 55 children born prematurely were examined; eye fundus information could be obtained by indirect ophthalmoscopy in all of them. The frequency of regressed retinopathy of prematurity was 35.45 percent for the whole group. Severe forms with optic atrophy, dragged optic disk, vitreoretinal scarring, retinal traction and temporal avascular retina were seen in 13.63 percent of cases. Moderate forms with pigmentary changes, vitreoretinal interphase changes and lattice degeneration were seen in 21.81 percent of cases. While the severe and moderate regressed premature retinopathy findings in premature children with gestational ages of 30-34 weeks were observed to be 12.0 and 14.0 percent, respectively, those in the 25-29 week-gestational-aged premature children were determined to be 5.0 and 28.33 percent, respectively. Although the incidence of both severe and moderate regressed premature retinopathy was higher in the 25-29 week gestational-aged group when compared to that of the 30-34-week-gestational-aged group, the difference was not found to be statistically significant ($p > 0.05$).

In conclusion, premature retinopathy should not only be followed up in the early stage with active changes but also later in infancy and childhood because of regressed premature retinopathy findings that may require treatment.

Key words: prematurity, regressed retinopathy of prematurity.

There are many hazards of preterm birth, and survivors are more prone to developing abnormalities of motor and sensory functions, including the visual system. retinopathy of prematurity (ROP) continues to be a serious problem in prematures despite improved possibilities of neonatal care, monitoring and treatment. The etiology is still unknown but several factors have been suggested to be involved in the development of the disease[1-3]. ROP, a proliferative inflammatory process attacking the developing retinal vessels during the perinatal period, remains one of the significant contributors to permanent morbidity in the premature population[4-7]. In its severest form, ROP progresses to total retinal detachment and blindness. In its milder forms, ROP is now known to leave ocular sequelae in the form of myopia and strabismus[8]. In the last decade important investigations have been made to prevent and dimish the severity of ROP[2,6]. We have conducted a retrospective study on premature children born in Sivas, Turkey during 1989-1992 in order to investigate the occurrence of ocular abnormalities. This paper deals with regressed ROP findings. A comparative study on the prevalence of visual impairments, refractive errors and ocular motility disorders in premature babies and a control grop of full-term babies will be reported separately.

Material and Methods

The study was performed in a well-defined geographical area, the Sivas region, on children born between January 1989-January 1992, with a birth weight < 2300 g and a gestational age < 34 weeks. The conditions for making such a study in the Sivas region were considered to be quite

favorable. We divided the premature children into two groups according to birth weight and gestational age. A total of 30 premature children constituted group I, whose gestational ages ranged between 25-29 weeks. Group II included a total of 25 premature children with gestational ages ranging from 30-34 weeks. At the age of 5-8 years, each child underwent a standard examination of visual function, ocular motility and ophthalmoscopic fundus appearance. Mydriatic drops (cyclopentolate hydrochloride 1%) were used to obtain a full view of the retinal periphery. The fundus was examined using the indirect binocular ophthalmoscope and a 20 diopter lens. A scleral depressor could not be used in any of the children aged 5-8 years. Exact information on fundus condition was available for 110 eyes of 55 premature children. In our classification of regressed ROP, we followed the suggestions of the International Committee for the Classification of Late Stage of ROP[9]. We have included in this study a subdivision into severe and moderate regressed ROP in order to differentiate the deegree of severity. The severe form included cases with vitreoretinal scarring equal to or larger than one optic disk diameter, optic atrophy, the presence of tangential traction of the retina, dragged optic disk and peripheral avascular retina. The remaining cases with ony pigmentary change, vitreoretinal interphase changes and lattice degeneration constituted the group of patients with moderate regressed ROP. We compared the incidence of the severe and moderate forms of ROP between the two groups. For statistical evaluation, "the significance of difference between the two groups' percentage method" was used.

Results

A total of 30 premature children constituted group I. Their gestational ages ranged between 25-29 weeks, the mean age being 27.8 ± 0.9 weeks. Of these, 16 (53.3%) were male and 14 (46.6%) female. At examination their ages varied between 5 and 8 years; the mean age was 6.7 ± 1.1 years. Their minimum, maximum and mean birth weights were 1100 g, 2000 g and 1617 ± 267 g, respectively. Group II included a total of 25 premature children. Their gestational ages ranged from 30 to 34 weeks and the mean age was 31.5 ± 1.3 weeks. Of these, 12 (48%) were male and 13 (52%) female. They were 5-8 years old, the mean age being 6.32 ± 1.18 years. Their minimum, maximum and mean birth weights were 1200 g, 2300 g and 1844 ± 367 g, respectively.

The results of the fndus examination of children performed by indirect opthalmoscopy are given in Table I.

Table I. Regressed Premature Retinopathy Findings in All Premature Children

	Group I n	(60 eyes) (%)	Group II n	(50 eyes) (%)
Normal	34	(56.66)	37	(74.0)
Optic atrophy	-	(-)	1	(2.0)
Scarring in the temporal peripheral retina	3	(5.0)	2	(4.0)
Increase in pigmentation in the temporal retina	13	(21.66)	5	(10.0)
Vitreoretinal interface anomalies	3	(5.0)	2	(4.0)
Dragged aptic disk	5	(8.33)	3	(6.0)
Temporal avascular retina	1	(1.66)	-	(-)
Lattice degeneration	1	(1.66)	-	(-)

While the fundus in 34 (56.7%) eyes in group I was observed to be normal, scarring in the temporal peripheral retina was found in three (5%) eyes, increase in pigmentation in the temporal retina in 13 (21.7%) eyes, dragged optic disk in five (8.3%) eyes, temporal avascular retina in one (1.7%) eye, lattice degeneration in one (1.7%) eye and vitreoretinal interface anomalies were noted in three (5%) eyes. As for group II, the fundus in 37 (74%) eyes was found to be normal while optic atrophy was observed in one (2%) eye, scarring in the temporal peripheral retina in two (4%) eyes, increase in pigmentation in the temporal retina in five (10%) eyes, dragged optic disk in three (6%) eyes, and vitreoretinal interface anomalies were noted in two (4%) eyes.

Regressed premature retinopathy findings were described in 26 (43.3%) of 60 eyes of 30 premature children in group I. In group II, regressed premature retinopathy findings were determined in 13 (26%) of 50 eyes of 25 premature children. As for the evaluation made without subdividing by gestational age, regressed premature retinopathy findings were encountered in 39 (35.5%) of 110 eyes of 55 premature children.

While the severe and moderate regressed premature retinopathy findings in group II were observed to be 12 and 14 percent, respectively, those in group I were determined to be 15 and

28.3 percent, respectively. Although in group I the incidence of both severe and moderate regressed premature retinopathy was higher than that of group II, the difference between the two groups' findings was not statistically significant ($t = 2.93$, $p > 0.05$).

Increase in pigmentation in the temporal retina was the most frequent ROP finding in both group I and group II, with a high incidence of 21.7 and 10 percent, respectively. Without taking the gestational age into consideration, an increase in pigmentation in the temporal retina was encountered in 18 (16.4%) of the 110 eyes of 55 premature children.

Discussion

Severe ROP, congenital cataract and optic atrophy account for vision loss in premature children[10]. Several studies from the United States have shown that the incidence of blindness from ROP in infants with birth weights of less than 1500 g ranges from 1.8 to 4.0 percent, but the distribution is markedly skewed towards those weighing less than 1000 g[11].

It is well established that ROP is commoner in premature babies of low birth weight than in others. In one study regressed ROP was seen in about two-thirds of the prematures with birth weights < 1000 g[12]. Similar findings were seen with regard to immaturity. More than half the children with a gestational age of < 30 weeks had ROP[12]. In preterm infants with a birth weight below 2000 g, a gestational age less than 36 weeks and a history of oxygen therapy, ROP should be investigated. Such an investigation may be made during the 7-9th week of life most satisfactorily. The pupilla of the infant is not well dilated earlier and vitreous blurring caused by the tunica vasculosa lentis leads to an insufficient viewing of the fundus. For this reason, ROP cannot be determined and a wrong diagnosis may be made if the fundus examination is made before the 7th-9th week of life. ROP may lead to varying retinal pathologies. When examining the pathological changes of the posterior segment, it is observed that it includes peripheral retinal pigmentation changes, vitreous blurring, peripheral retinal lacerations and lattice degeneration, fibrous bands in the temporal peripheral retina, retinal blood vessel retractions, retrolental fibrovascular membranes, retinal detachment, retinal traction, vitreoretinal scarring, deformations in the optic disk and similar lesions[13].

In 80 percent of infants, ROP regresses spontaneously and may occasionally have a few sequelae. In the remaining approximately 20 percent of infants, complications related to scarring may develop following active ROP[13]. While some of these complications may not be significant at all, others may be etremely serious and even lead to loss of vision[14,15].

The International Committee for the Classification of Late Stages of ROP has pointed out that regressed ROP has a broad spectrum of eye fundus abnormalities[9]; we clasisfied them in two groups as severe and moderate. The severe form included cases with vitreoretinal scarring equal to or larger than one optic disk diameter, optic atrophy, the presence of tangential traction of the retina, dragged optic disk and peripheral avascular retina. The remaining cases with only pigmentary changes, vitreoretinal interphase changes and lattice degeneration constituted the group of patients with moderate regressed ROP.

In one study, regressed ROP was seen in about 30 percent of children with birth weights < 1000 g, but in 45.5 percent in the total group[12]. Moderate forms with pigmentary changes and/or vitreortinal interphase changes were found in 35.8 percent. Pigmentary changes were the most common signs of regressed ROP. Severe forms with vitreoretinal scarring and retinal traction were seen in 9.7 percent[12].

The incidence of severe, moderate and total regressedd ROP findings in our study as well as in several other studies is shown in Table II.

Table II. Incidence of Severe, Moderate and Total Regressed ROP Findings in Our and Several Other Studies

	Severe ROP (%)	Moderate ROP (%)	Total ROP (%)
Present Study	13.63	21.81	35.45
Gallo et al.[12]	9.70	35.80	45.50
Priscilla et al.[16]	7.8	6.9	10.0
McGinnity et al.[17]	3.0	3.7	6.7

There is a very significant relation between neurological development and ROP. Following investigations, it has been established that

hypoperfusion episodes in the cerebral blood circulatilon lead to cerebral ischemia. In addition, the ocular blood flow decreases, increasing the existing retinal ischemia. As a result, the severity of premature retinopathy increases[14]. The association between periventricular hemorrhage, periventricular leukomalacia, extensive cerebral parenchymal changes proven by ultrasound examination and ROP was interesting but not statistically significant[10]. Damage to the retina by light (especially blue spectrum of light) has also been implicated in the pathogenesis of ROP[18].

Risk factors for regressed ROP are extreme prematurity, extremely low birth weight, severe respiratory distress syndrome and intraventricular hemorrhage. According to Brown et al.[19], when the critically ill preterm infants were examined, intraventricular hemorrhage and convulsions were higher in ratio in the group with scarring ROP than in the group without. It has been suggested that there may be a close association among regressed ROP, high-grade myopia and ischemic brain lesions[10]. In one study[20], it was observed that asphyxia in preterm infants was associated with poor visual prognosis. Of the 607 preterm infants, 48 percent had acute ROP. Spontaneous resolution occurred in most cases and only six of the infants developed scarring ROP[20].

With regard to the ophthalmoscopic findings, pigmentary changes were the commonest signs of regressed ROP, in 37.3 percent of cases[12]. In this study, pigmentation changes in the peripheral retina were found in 21.7 percent of cases in the severe premature group. As for the mild premature group, this ratio was 10.0 percent. Without taking the gestational age into consideration, an increase in pigmentation in the temporal retina was encountered in 18 (16.36%) of 110 eyes of 55 premature children.

The high frequency of regressed ROP in our material strongly indicates that prematurely born children are an ophthalmological risk group, with increased incidence of retinal complications. They must therefore be carefully followed up during the period of visual development in order to prevent visual dysfunction with intervention as early as possible.

Finally, pediatricians and ophthalmologists must continue to jointly investigate the conditions that predispose to ROP in the hope of preventing or at least diminishing the severity of the disease.

REFERENCES

1. Purohit DM, Ellison RC, Zierler S, Miettinen OS, Nadas AS. Risk factors for retrolental fibroplasia: experience with 3,025 premature infants. Pediatrics 1985; 76: 339-344.
2. Becker H, Lieser K, Heller K. Einfluss und Zusammenhang verschiedener Risikofaktoren bei der Enststehung der Retinopathia praematurorum. Klin Monatsbl Augenheilkd 1990; 196: 456-459.
3. John E, Todd DA. Patent ductus arteriosus and ROP in infants below 27 weeks gestation. Aust Paediatr J 1988; 24: 171-173.
4. Phelps DL. ROP: An estimate of vision loss in the United States. Pediatrics 1979; 67: 924-925.
5. Cats BP, Tan KE. Prematures with and without regressed retinopathy of prematurity: comparison of long-term (6-10 years) ophthalmological morbidity. J Pediatr Ophthalmol Strabismus 1989; 26: 271-275.
6. Hungerford J, Stewart A, Hope P. Ocular sequelae of preterm birth and their relation to ultrasound evidence of cerebral damage. Br J Ophthalmol 1986; 70: 463-468.
7. Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. Br J Ophthalmol 1983; 67: 302-305.
8. Jacqueline MP, Suzan S, Hilary EA, Patricia H. Ocular sequelae in premature infants. Pediatrics 1993; 92: 787-790.
9. Committee for the Classification of the Late Stages of ROP. An International Classification of ROP. Arch Ophthalmol 1987; 105: 906-912.
10. Tuppurainen K, Herrgaord E, Martikainen A, Mäntyjärvi M. Ocular findings in prematurely born children at 5 years of age. Arch Clin Exp Opthalmol 1993; 231: 261-266.
11. Gunn TR, Easdown J, Outerbridge EW, Aranda JV. Risk factors in retrolental fibroplasia. Pediatrics 1980; 65: 1096-1100.
12. Gallo JE, Lennerstrand G. A population-based study of ocular abnormalities in premature children aged 5 to 10 years. Am J Ophthalmol 1991; 111: 539-547.
13. Kanski JJ. Clinical Ophthalmology: A Systematic Approach. London: Butterworth-Heinemann Ltd; 1989: 243.
14. Fledelius HC. Ocular features other than retinopathy of prematurity in the infant. Acta Ophthalmol 1990; 68: 214-217.
15. Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. Br J Ophthalmol 1983; 67: 302-305.

16. Priscilla B, Johnson A. Ocular defects in infants of extremely low birth weight and low gestational age. Br J Ophthalmol 1991; 75: 84-87.

17. McGinnity FG, Donzis P. Myopia associated with retinopathy of prematurity. Ophthalmology 1986; 93: 1593-1598.

18. Dowdeswell HJ, Slaterr AM, Broomhall J, Tripp J. Visual deficitis in children born at less than 32 weeks' gestation with and without major ocular pathology and cerebral damage. Br J Ophthalmol 1995; 79: 447-452.

19. Brown DR, Milley JR, Ripepi UJ, Biglan AW. Retinopathy of prematurity. ROP. Risk factors in a five-year cohort of critically ill premature neonates. Am J Dis Child 1987; 141: 154-160.

20. Fielder AR, Moseley MJ, Ng YK. The immature visual system and premature birth. Br Med Bull 1988; 44: 1093-1118.

Neurological soft signs and EEG findings in children and adolescents with Gilles de la Tourette syndrome

Z. Bengi Semerci

[1]Department of Child and Adolescent Psychiatry, Hacettpe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Semerci ZB. Neurological soft signs and EEG findings in children and adolescents with Gilles de la Tourette syndrome. Turk J Pediatr 2000; 42; 53-55.

Gilles de la Tourette syndrome (GTS) is a childhood-onset neuropsychiatric disorder, characterized by multiple motor and vocal tics. The presence of EEG abnormalities and neurological soft signs are reported in patients with GTS. In this study, conducted on 40 children and adolescents, non-specific EEG abnormalities and neurological soft signs were detected in 12 and 57.5 percent of cases, respectively. These findings are analyzed in comparison with other neuropsychological test results. A statistically significant association between EEG abnormalities, neurological soft signs and low-performance IQ results was detected.

Key words: EEG, neurological soft signs, Gilles de la Tourette syndrome.

Gilles de la Tourette syndrome (GTS) is a childhood-onset neuropsychiatric disorder, characterized by multiple motor and vocal tics. Its symptoms can show variations during the disease course. Motor tics vary from simple abrupt movements, such as eye blinking and head jerks, to more complex behaviors such as facial expressions or gestures of the face or hands. Vocal tics range from simple throat clearing to fragments of speech including isolated words. Onset age of Tourette's syndrome is around seven years old. GTS improves during late adolescence and early adulthood[1,2].

The etiology of GTS is not entirely known today, although some hypotheses exist in the literature[3]. The results of neuroanatomical, neuropathological and neuroradiological studies demonstrate a posible role of basal ganglia and the structures which are connected to basal ganglia, such as the thalamic and cortical regions, in the pathogenesis of GTS.

Electroencephalogram (EEG) abnormalities were oserved in 12-37 percent of GTS cases. However, they were not specific for GTS, and no correlation was shown between tics and paroxysmal activities[2]. These findings support the hypothesis that the tics originate from the subcortical structures, such as basal ganglia, rather than from cortical structures[4].

In some studies, it was demonstrated that patients with GTS have neurological soft signs, the most common being minor motor asymmetry, coordination problems, nystagmus and reflex asymmetry[5]. The "neurological soft sign" has been used to describe various abnormalities on the neurological examination that are not believed to be part of a well-defined neurological syndrome[6]. The validity of soft signs would be supported if they predicted motor abnormalities across development. Soft signs were predicted at age seven and over[6].

The aim of this study was to evaluate neurological soft signs and EEG findings in children with GTS, and to look for a correlation of these parameters with other neuropsychiatric tests.

Material and Methods

Forty children and adolescents, who were diagnosed as GTS according to DSM-IV[7] criteria, were enrolled in the study. Eleven (27.5%) of the subjects were female and 29 (72.5%) were male. Their ages ranged between 7-15 years (mean ± sd = 109 ± 2.4).

All patients were examined by the Pediatric Neurology Department for the presence of additional neurological findings. Neurological soft signs were determined in 33 children by a child and adolescent psychiatrist. Neurological soft signs included the ability to differentiate right and left, both according to themselves and the observer; hand-eye coordination; simultaneous double stimuli; coordinated movement; and finger following.

Electroencephalogram, WISC-R inteligence test and Bender-Visual-Motor Perceptions test[8] were performed. The severity was assessed by the Yale Global Tic Severity Scale[9] (YGTSS). Information about the sociodemographical status of the patients was collected via a questionnaire prepared by the researcher. Statistical analysis was performed with a computer package program (Statistical Package for Social Sciences, For Windows Release 5.0.1, SPSS Inc., 1992). Chi-square test was used with non-parametric data and two tailed t-test with parametric data. Fisher's exact test was applied when necessary.

Results

Electroencephalogram (EEG) analysis was done on all 40 patients enrolled in the study. Thirty-five had normal EEG findings, whereas in five patients a dysrhythmia in basal activity was observed. There was no statistically significant difference between males and females (X^2: 0.1572 DF:1 P = 0.6918).

When EEG findings were compared with WISC-R test results, an association between EEG abnormalities and low performance scores on the WISC-R test was observed (P = 0.049). There was no statistically significant association between the results of the Bender tests and EEG findings (P = 0.66).

The right-left preferences of the 33 children and adolescents in using their hands, feet and eyes are shown in Table I. The distribution of neurological soft signs according to subgroups is shown in Table II. Twenty-three (57.5%) of the children and adolescents had a problem in one of the subgroups of straight and cross right-left differentiation, simultaneous double stimuli, hand-eye coordination, balance and coordinated movements and finger following. Ten (25%) of the subjects had no problem.

Table I. Preferences of Children and Adolescents with GTS in Using Their Hands, Feet, and Eyes (According to Gender)

	Right			Left		
	F	M	Total	F	M	Total
Hand	10	22	32	0	1	1
Foot	7	19	26	3	4	7
Eye	7	16	23	3	7	10

Table II. Distribution of Neurological Soft Signs (According to Subgroups)

	EEG	
Neurological soft signs	Normal	Abnormal
Right-left differentiate	20	13
Cross right-left differentiate	16	17
Simultaneous double stimuli	26	7
Hand-eye coordination	29	4
Coordinated movement	25	8
Finger following	33	0

During the analysis of the presence of a relationship between neurological soft signs and other variables, a statistically significant Verbal IQ > Performance IQ difference was found in the WISC-R test (U = 19.0, P = 0.038). No statistically significant association was observed between nerological soft signs and EEG findings (Table III).

Table III. Comparison of Neurological Soft Signs with EEG

	EEG	
Neurological soft signs	Normal	Abnormal
Negative	9	1
Positive	20	3
Missing	6	1

X^2: 0.0763, DF: 1, P = 0.7824 (ad).

Discussion

Few studies in the literature have investigated the presence of neurological soft signs in Tourette's syndrome. Neurological soft signs might be significant in the detection of lateralization, which is thought to play a role in the pathogenesis o GTS[10]. In our study, 32 (96.9%) of the patients enrolled in the study were right-handed and some neurological soft signs, particularly right-left differentiation, were observed in 57.5 percent of the patients. Neurological soft signs have been associated with hyperactivity, conduct, and emotional and cognitive disorders[6]. Performance IQ scores were lower than verbal IQ scores based on WISC-R test results (Verbal IQ = 92.5 ± 18.8, Performance IQ = 88 ± 19.3). This phenomenon is observed in either right-sided or bilateral cerebral hemispheric disorders[11-13]. GTS patients in this study showed a pattern of lower amplitude and impaired visual-motor perceptions and complex motor processing as observed in cross right-left differentiation, simultaneous double stimuli and hand-eye coordination. These deficits have been associated with various anterior-cortical-subcortical systems[14].

Non-specific EEG abnormalities were reported within the rates ranging from 12 to 95 percent[15]. The frequency of EEG abnormalities, all of them non-specific, was five percent in our study group. Trimble[15] reported the presence of EEG abnormalities in 13 percent cases and a low frequency of neurological soft signs in a clinical series consisting of 53 patients. On the other hand, Neufeld et al.[16] did not detect any significant difference in the frequency of EEG abnormalities between patient and control groups. Drake et al.[17], using a computer-aided EEG analysis, found their patients to be free of EEG abnormalities with conventional EEG methods, and observed abnormal recordings in four of 30 patients. Non-specific EEG abnormalities do not appear to be an important parameter in the diagnosis and follow-up of GTS patients when the prevalance of these abnormalities in the general population is taken into account.

These results suggest that neurological soft signs and neuropsychiatric (WISC-R, Bender-Gestalt) test might be important in the evaluation of the pathogenesis and clinical follow-up of GTS patients.

REFERENCES

1. Apter A, Pauls DL, Belich A, et al. An epidemiologic study of Gilles de la Tourette's syndrome in Israel. Arch Gen Psychiatry 1993; 50: 734-738.
2. Robertson MM. Annotation: Gilles de la Tourette syndrome-an update. J Clin Psychol Psychiatry 1994; 35: 597-611.
3. Leckman JF, Peterson BS, Anderson GM, et al. Pathogenesis of Tourette's syndrome. J Child Psychol Psychiatr 1997; 38: 119-142.
4. Steingard R, Dillon-Stout D. Tourette's syndrome and obsessive-compulsive disorder. Psychiatr Clin North Am 1992; 15: 849-860.
5. Robertson MM. The Gilles de la Tourette syndrome: the current status. Br J Psychiatry 1989; 154: 147-169.
6. Pine DS, Scott MR, Busner C, et al. Psychometrics of neurological soft signs. J Am Acad Child Adolesc Psychiatry 1996; 35: 509-515.
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th ed). Washington, D.C., American Psychiatric Association, 1994.
8. Koppitz EM. The Bender-Gestalt test for children: a normative study. J Clin Psychology 1960; 16: 432-435.
9. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Child Adolesc Psychiatry 1988; 28: 566-573.
10. Robertson MM, Trimble MR, Less AJ. The psychopathology of the Gilles de la Tourette syndrome: a phenomenological analysis. Br J Psychiatry 1988; 152: 383-390.
11. Lanser JB, Van Santen HC, Jennekens-Schinkel A, Roos RA. Tourette's syndrome and right hemisphere dysfunction. Br J Psychiatry 1993; 163: 116-118.
12. Brookshire BL, Butler IJ, Ewing-Cobbs L, et al. Neuropsychological characteristics of children with Tourette syndrome: evidence for a nonverbal learning disability? J Clin Exper Neuropsychology 1994; 16: 289-302.
13. BomnsteinRA, Moterazzo JD. Wechsler VIQ versus PIQ differences in cerebral dysfunction: a literature review with emphasis on sex differences. J Clin Neuropsychol 1992; 4: 319-334.
14. Volkmar FR, Leckman JF, Detlor J, et al. EEG abnormalities in Tourette syndrome. J Am Child Adolesc Psychiatry 1984; 23: 352-353.
15. Trimble M. Psychopathology and movement disorder: a new perspective on the Gilles de la Tourette syndrome. J Neurol Neurosurg and Psychiatry 1989; (Special suppl): 90-95.
16. Neufeld MY, Berger Y, Chopman J. Routine and quantitative EEG analysis in Gilles de la Tourette's syndrome. Neurology 1990; 40: 1837-1839.
17. Drake ME, Hietter SA, Padamandan H, et al. Computerized EEG frequency analysis in Gilles de la Tourette syndrome. Clin Electroencephalogr 1991; 22. 250-253.

Solitary rectal ulcer syndrome in children

İrfan Kırıştıoğlu[1], Emin Balkan[1], Nizamettin Kılıç[1], Hasan Doğruyol[1]

[1]Department of Pediatric Surgery, Uludağ University Faculty of Medicine, Bursa, Turkey

SUMMARY: Kırıştıoğlu İ, Balkan E, Kılıç N, Doğruyol H. Solitary rectal ulcer syndrome in children. Turk J Pediatr 2000; 42: 56-60.

The solitary rectal ulcer syndrome (SRUS) is an unusual disorder in childhood. Although well recognized in adult literature, the pediatric experience with this condition is limited, so SRUS often goes unrecognized or misdiagnosed. There are very few pediatric case reports in the English literature.

This report describes four patients who presented with rectal bleeding, constipation, mucous discharge, and lower abdominal pain, with a diagnosis of SRUS. The diagnosis was made by rectoscopy, defecogram, anorectal manometry and histopathological evaluation. In two patients, defecogram showed a rectocele with both, the sphincter failed to relax to voluntary squeeze pressure on anorectal manometric examination. the histopathological finding in all patients was fibrous obliteration of the lamina propria with disorientation of muscle fibers. all of the patients responded well to conservative therapy, which included defecation training, laxatives, sulfasalazine, and application of rectal sucralfate enema, and remained asymptomatic on the follow-up.

Although rare in the pediatric population, SRUS should be relatively easy to recognize in the child with rectal bleeding, after elimination of other causes. If suspected, the diagnosis of SRUS may be made at endoscopy and confirmed by rectal biopsy.

Key words: solitary rectal ulcer syndrome, rectal bleeding, constipation, children.

Although, solitary rectal ulcer syndrome (SRUS) was described as early as the 19th century by Cruveilhier[1], the first definitive descriptions were made by Madigan and Morson in 1969[2]. The condition is rare, with an estimated annual incidence of one per 100,000 per year in the adult population[3]. The average age at presentation is around 30 years, but this condition can occur from adolescence to late middle age. It is even more unusual in childhood. The incidence of SRUS in children is unknown. We found only seven patients reported separately in the English literature. The clinical features of these cases are summarized in Table I[4-8]. Herein, we describe the clinical, radiological, and pathological features of four cases of SRUS occurring in children.

Case Reports

Case 1

An 11-year-old girl was referred because of intermittent rectal bleeding for four months. She had a history of straining during defecation, lower abdominal pain, and passage of mucus on defecation. Digital examination of the rectum revealed an enduration on the posterolateral rectal wall. test for intestinal parasites, including amebiasis, were negative. Sigmoidoscopy revealed an ulcer 2 to 6 cm in diameter on the posterolateral rectal wall 5 cm from the anal verge with well demarcated edges. Subsequent colonoscopic examination up to the cecum revealed no other lesions. An air contrast barium enema was normal, but evacuation of the barium was difficult. Anal manometry showed failure of he sphincter to relax to voluntary squeeze pressure (Fig. 1). Defecogram showed occult internal prolapse as well as a small posterior rectocele (Fig. 2). The first biopsy was reported as a non-specific granulation tissue of the rectum. The child was started on stool softener. A month later, a second sigmoidoscopy was performed because of the persistence of symptoms, and serial biopsies were repeated. These biopsies were reported as a solitary rectal ulcer (Fig. 3). After treatment with laxatives,

sulfasalazine, and defecation training for three months, the patient was asymptomatic, although the rectoscophic appearance remained unchanged. For the subsequent six months, she underwent reinvestigation of rectoscopy every month. During this period, although she was asymptomatic, a limited healing was observed by rectoscopy. Consequently, she was started on sucralfate enema in glycerine 10%, three times per day. After one month of local sucralfate application, the ulcer had shrunk significantly on endoscopic examination. After an additional three months of therapy with sucralfate enema, the ulcer had completely healed.

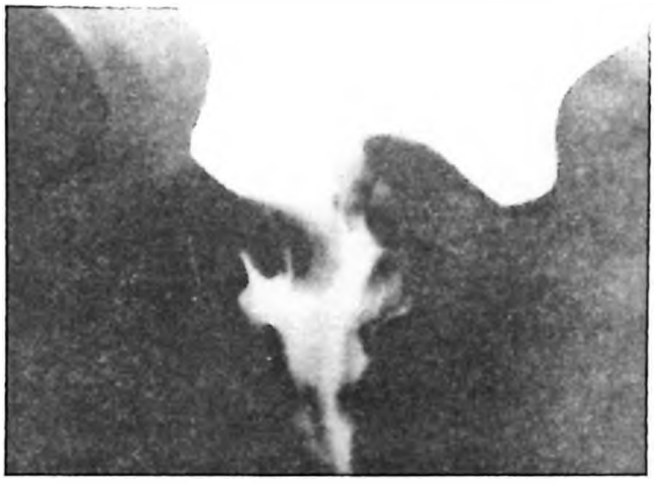


Fig. 1. Defecogram. Note the internal rectal intussusception and enterocele.

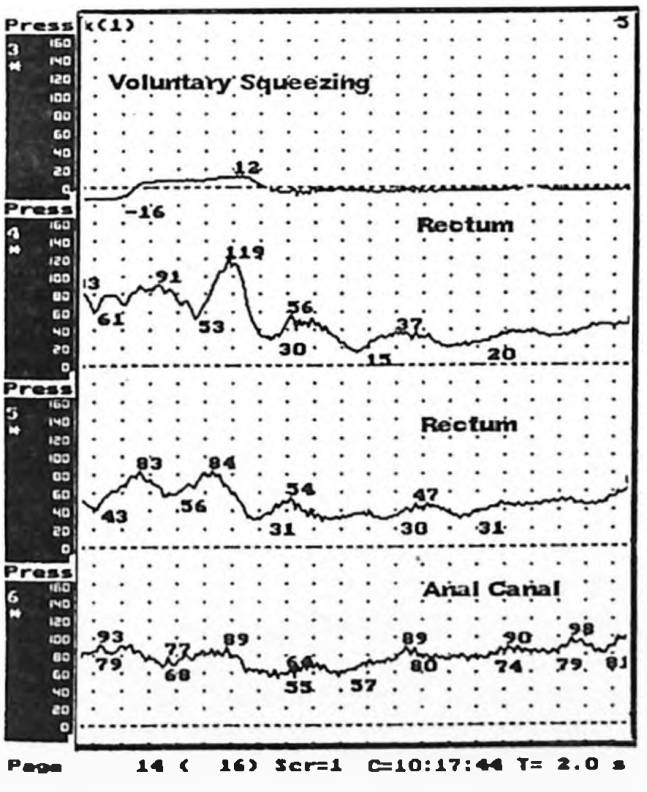


Fig. 2. Computerized anorectal manometry: no relaxation of pelvic musculature during squeezing.

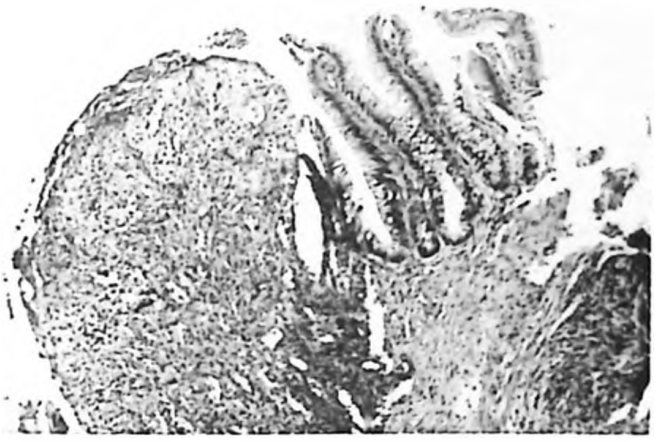


Fig. 3. Histological appearance of SRUS. The lamina propria is replaced by fibromuscular tissue. There are distorted crypts in the submucosa and superficial ulcerationn (H & E, x200).

Case 2

An eight-year-old girl presented with a small amount of rectal bleeding after defecation and lower abdominal pain. Previous complaint of the patient was chronic constipation for three months, which had been treated with defecation training and laxatives in another clinic. At the beginning of rectal bleeding, she was transferred to our institution. She was otherwise asymptomatic. Digital rectal examination was normal. Sigmoidoscopy showed an ulcer 0.5 to 1 cm on the posterolateral rectal wall 5 cm from the anal verge. Defecogram and anal manometric evaluation were normal. Histopathological examination revealed fibrosis of the lamina propria, ulceration and inflammatory cells infiltration. The ulcer healed three months after the initial episodes of bleeding, following treatment with laxatives and a high-fiber diet.

Case 3

An eight-year-old girl was referred because of constipation, rectal bleeding and rectal and lower abdominal pain during defecation. The physical examination was normal, except for sensation of the posterior rectal wall on rectal examination. During the rectoscopy, an ulcer 0.5 to 1 cm in diameter was seen on the right posterolateral rectal wall and a biopsy was taken. Defecogram showed an anterior rectocele 3.5 cm from the anorectal junction. The anorectal manometric examination showed that anal canal resting pressure was high and remained unchanged during squeezing. Pathology was

reported as a solitary rectal ulcer. Three months later after a conservative treatment, the ulcer was healed on endoscopic examination.

Case 4

A three-year-old-boy was referred because of a six-month history of constipation and soiling. Recently he had rectal bleeding and mucous discharge. The physical and rectal examinations were normal. Sigmoidoscopy showed an ulcer 0.5 to 1.5 cm in diameter surrounded by a hyperemic halo and covered with a fibrinous membrane on the posterior rectal wall 3.5 cm from the anal verge. Rectal biopsy was taken from the edge of the ulcer, and solitary rectal ulcer was confirmed by histopathological examination. The child was started on a high-fiber diet and laxatives. After one month of therapy, his symptoms disappeared and by the twelfth week the ulcer had almost healed.

Discussion

Solitary rectal ulcer syndrome is an unusual cause of rectal bleeding in children[9]. Only seven separate pediatric cases have been reported[1,4,5-8]. The largest series of solitary rectal ulcer patients, among those published by different authors, contain six extra pediatric cases (under 15-years-old)[2,10-12]. In these published series, none of the pediatric cases have been evaluated separately.

The etiology of the disorder remains obscure. Early report hypothesized that local proctitis or hamartomatous malformation in the rectal wall led to development of local ulcers, but no theory has been generaly accepted[6,13]. Recently, however, the common histological characteristic of the polypoid and ulcer lesions, as well as the characteristic history of straining and prolapse, have suggested that either local trauma or ischemia of the rectal wall is the common cause[10-15]. In normal circumstances, straining induces inhibition of the puborectalis muscle, but Rutter[15] showed increased electromyographic activity in patients with SRUS. Womack et al.[16] also reported increased intrarectal pressures during voiding. The significance of this finding is unknown, but it is stated that it has a traumatic effect on the rectal mucosa. Schweigher and Alexander-Williams[17] suggested that the SRUS is due to a preexisting rectal prolapse which itself may lead to further difficulty in defecation and also to secondary mucosal damage. The latter would result in increased mucus production and bleeding. In addition, patients with SRUS show failure of the sphincter to relax in response to voluntary squeeze pressure on manometric evaluation[4]. Most authors note two main causes of this mucosal lesion: rectal prolapse or intussusception and an abnormal relaxation of the pelvic muscles during defecation[4,16,17]. Two of our four patients had both rectocele and a high anal resting pressure without relaxation of the anal sphincter during squeezing. It is therefore suggested that SRUS is a weakening of the rectal wall caused by rectal prolapse or spastic pelvic floor syndrome, or both, in children. The most frequent symptoms are rectal bleeding, mucous discharge, tenesmus, and pain localized to the perineum or sacral area. It is common to find in these patients a long history of constipation, straining at defecation, and rectal prolapse, but these symptoms are non-specific and may be present with any other anorectal disease. In assessing the seven reported pediatric patients in whom sufficient clinical detail is available, only minor differences from adult patients are apparent[10,12,13]. In our patients, a small amount of rectal bleeding associated with constipation was the initial symptom.

Diagnosis of SRUS is made by rectoscopy, which also permits biopsy. The ulcers vary in size from a few milimeters up to 5 cm. The lesion is usually found on the anterior wall of the rectal mucosa. The posterolateral quadrants are rarely the site of ulcers. The distal point of the ulcers in children varies from 3 to 20 cm from the anal verge[4-8]. In our patients, all ulcers were seen on the posterior or posterolateral rectal wall and the distance of the ulcers from the anal verge varied from 3.5 to 11 cm. The significance of this localization is obscure. The varied macroscopic appearance of the rectal lesions that included mucosal hyperemia, ulceration, and/or polypoid lesion can be confusing. In addition, the rectal lesion can be multiple or circumferential[2,12]. Thus, an unusual-appearing rectal lesion with atypical presentation should arouse the suspicion of SRUS. The presence of rectal prolapse should further suggest a diagnosis of SRUS[4,7,13,16]. In our patients, the rest of the rectal mucosa was quite normal: there was no granular appearance or squamous metaplasia. The most common clinical diagnostic confusion is with inflammatory bowel disease or inflammatory cloacogenic polyp (ICP), which is

a rare polypoid lesion arising in the region of the anorectal transitional zone[14]. The most characteristic histopathological feature of SRUS is obliteration of the lamina propria of the mucous membrane in the region of the ulcer by fibroblasts and muscle fibers derived from the muscularis mucosae[2,12,14]. It is important to distinguish the histopathological appearances of SRUS. from inflammatory bowel disease, infectious proctocolitis and cloacogenic polyp. The major difference between ICP and SRUS relates to the site, but they share similar histopathological features. Furthermore, if a biopsy is taken from the proximal end of an ICP and does not include the squamous eithelium of the anal canal, it can be incorrectly reported as SRUS[14]. Although it is thought that these two clinical entities are manifestations of the same pathogenetic process, i.e., mucosal ischemia secondary to prolapse leading to the decribed histological changes[14,18], this theory has not yet been accepted. In three of our patients, the first rectal biopsy was histologically suggestive of solitary ulcer. In the other case, the first biopsy was reported as a non-specific granulation tissue, but the second biopsy showed classic histopathological findings of SRUS. All biopsies had ganglion cells and none had specific findings of neuronal intestinal dysplasia.

The most appropriate treatment of this conditionhas not yet been determined. Treatment of SRUS is difficult and should be conservative as far as possible. Conservative treatment of SRUS includes a high residue diet, stool softeners, and defecation training[5,6,8,10,11,13]. Most studies have suggested that sulfasalazine and topical steroids are of no significant benefit to these patients[10,12,13]. Sucralfate has been shown to be effective in the treatment of peptic ulcer, esophagitis, and post-polypectomy hemorrhage. Batman et al.[19], and Spiliadis et al.[20] showed that sucralfate enema might be effective in the teratment of SRUS. Symptomatic improvement and healing after medical therapy such as a high residue diet, laxatives, and defecation training were obtained in three of our four patients. Although the other patient was totally asymptomatic after three months of conservative therapy, endoscopic healing of the ulcer was completed after one year of treatment. Sucralfate enema was successfully used in this patient.

Although local excision, insertion of a Thiersch wire, a different kind of abdominal rectopexy and colostomy have been recommended as operative treatment in adults[12,13,17,21], none of these procedures is free of complication. A laser therapy has recently been recommended by some authors[22]. In the pediatric age group, conservative therapy should be considered as a first choice of treatment. We successfully treated our patients using conservative treatment.

The recognition of solitary rectal ulcer is relatively easy in adults because of the lower localization of the lesion and different macroscopic appearance of the SRUS, but diagnosis is somewhat difficult in children. Since the localization of the lesion is important in children, careful endoscopic examination is necessary. If the ulcer does not respond to classical medical therapy, the sucralfate enema may also be used.

Acknowledgement

We are greatful to Dr. Sema Özuysal for examining the histological specimens.

REFERENCES

1. Cruveilhier J. Ulcere chronique du rectum. Anat Path 1870; 2: 4.
2. Madigan MR, Morson BC. Solitary ulcer of rectum. Gut 1969; 10: 871-881.
3. Martin CJ, Parks TG, Biggart JD. Solitary rectal ulcer syndrome in Northern Ireland 1971-1980. Br J Surg 1981; 68: 744-747.
4. Eigenmann PA, Coultre CL, Cox J. Solitary rectal ulcer: an usual cause of rectal bleeding in children. Eur J Pediatr 1989; 152: 658-660.
5. Figueroa-Colon R, Younozasi MK, Mitrops FA. Solitary rectal ulcer syndrome of rectum in children.J Pediatr Gastroenterol Nutr 1989; 8: 408-412.
6. Gündoğdu ZH, Altin MA, Aksoy F. Solitary rectal ulcer in a 12-year old girl: an unusual cause of rectal bleeding. Pediatr Surg Int 1994; 9: 131-132.
7. Rubia LD, Villaespesa AR, Cebrero MC. Solitary rectal ulcer syndrome in a child. J Pediatr 1993; 122: 733-735.
8. Sondheimerr JM, Slagle TA, Bryke CR. Solitary rectal ulcer syndrome in a teenaged boy. J Pediatr Gastroenterol Nutr 1985; 4: 835-838.
9. Balkan E, Kırıştıoğlu İ, Gürpınar A, Özel İ, Sınmaz K, Doğruyol H. Sigmoidoscopy in minor lower gastrointestinal bleeding. Arch Dis Child 1998; 78: 267-268.
10. Brant-Gradel VV, Huibregtse K, Tytggat GN. Treatment of solitary rectal ulcer syndrome with high-fiber diet and abstention of straining at defecation. Dig Dis Science 1984; 29: 1005-1008.
11. Ford MJ, Anderson JR, Gilmour HM. Clinical spectrum of solitary ulcer of the rectum. Gastroenterol 1983; 84: 1533-1540.

12. Tjandra JJ, Fazio VW, Petras RE. Cinical and pathologic factors associated with delayed diagnosis in solitary rectal ulcer syndrome. Dis Colon Rec 1993; 36: 146-153.
13. Niv L, Bat L. Solitary rectal ulcer syndrome: clinical, endoscopic, and histologic spectrum. Am J Gastroenterol 1986; 81: 486-491.
14. Bass J, Souchy P, Walton M. Inflammatory cloacogenic polyps in children. J Pediatr Surg 1995; 30: 585-588.
15. Rutter KR. Solitary rectal ulcer syndrome. Proc R Soc Med 1975; 68: 22-26.
16. Womack NR, Williams NS, Holmfield JH. Pressure and prolapse-the cause of solitary rectal ulceration. Gut 1987; 28: 1228-1233.
17. Schweigher M, Alexander-Williams J. Solitary ulcer syndrome of rectum its association with occult rectal prolapse. Lancet 1977; 1: 170-171.
18. Washington K, Rourk MH Jr. Inflammatory cloacogenic polyp in a child: part of the spectrum of solitay rectal ulcer syndrome. Pediatr Pathol 1993; 13: 409-414.
19. Batman F, Arslan S, Telatar H. Effect of sucralfate enema in the treatment of solitary rectal ulcer. Endoscopy 1988; 20: 128.
20. Spiliadis C, Skandalakis N, Emmanouliadis A. Treatment of solitary rectal ulcer syndrome with sucralfate enema. Gastrointest Endosc 1989; 35: 131-132.
21. Tjanda JJ, Fazio VW, Church JM. Ripstein procedure is an effective treatment for rectal prolapse without constipation. Dis Colon Rec 1993, 36: 501-507.
22. Rau BK, Harikrishnan KM, Krishna S. Laser therapy of solitary rectal ulcers: a new concept. Ann Acad Med Singapore 1994; 23: 27-28.

Cyclic neutropenia complicated by renal AA amyloidosis

Ayşe Metin[1], Fügen Ersoy[1], Keriman Tınaztepe[1], Nesrin Beşbaş[1], İlhan Tezcan[1], Özden Sanal[1]
[1]Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Metin A, Ersoy F, Tınaztepe K, Beşbaş N, Tezcan İ, Sanal Ö. Cyclic neutropenia complicated by renal AA amyloidosis. Turk J Pediatr 2000; 42: 61-64.

Cyclic neutropenia is a rare disease characterized by regular cyclic fluctuations in the numbers of neutrophils. Patients with the disease suffer from recurrent infections at regular intervals of nearly three weeks. Recently, recombinant human granulocyte colony-stimulating factor (rhG-CSF) was reported to be an effective treatment for this disease. here we describe 17-year-old cyclic neutropenic female patient with a very rare asociation of renal amyloidosis of AA type who was under intermittent rhG-CSF treatment for the previous one and a half years. We conclude that although the disorder is usually benign, reactive amyloidosis may rarely develop in cases who remain untreated for a long period of time. However familial Mediterranean fever (FMF) type II should also be born in mind, particularly in predisposed populations.

Key words: cyclic neutropenia, AA type amyloidosis, renal, childhood.

Cyclic neutropenia is characterized by a history of repetitive infectious complications due to cyclic ossilations in the number of circulating neutrophils. Cyclic neutropenia affects children of both sexes and shows a genetic basis in approximately 25 percent of cases, being most commonly autosomal dominant with variable expression. Between neutropenic periods, patients usually remain free of infection[1].

Although this disorder is usually benign, death from overwhelming infection can occur in as many as 10 percent of affected patients. Clostridium perfringens is reported as one of the more common microorganisms. Some patients may experience clinical improvement as they grow older with the cycles becoming less noticeable and symptoms less conspicuous. The disorder is lifelong and does not predispose to leukemia or aplastic anemia[1].

Here we describe a patient with cyclic neutropenia who developed renal amyloidosis of reactive, AA type under the therapy of recombinant human granulocyte-colony stimulating factor (rhG-CSF).

Case Report

The patient (A.E.), 4.5-year-old female, was referred to hacettepe University Children's Hospital in May 1986 because of an absence of granulocytes on blood count. She had been suffering from recurrent severe aphthous gingivostomatitis, swelling of lips, fever, tonsilitis, otitis and sinusitis since her earliest childhod. She was followed-up by local physicians and treated successfully with antibiotics. The patient was a term, 3400 g product of unrelated parents. She had three healthy older sisters and her family history was unremarkable. On admission she was diagnosed as having pneumonia and otitis media and treated with antibiotics. Routine laboratory examinations revealed a moderate leukopenia (WBC count was 4000 cells/μl) with absolute granulocytopenia with monocytosis (0% neutrophils, 82% lymphocytes, 2% eosinophils and 15% monocytes; platelets were normal). Bone marrow studies revealed an arrest of myelopoiesis at the myelocytic stage with an absence of bands and segmented neutrophils. There were no signs of myelodysplasia and the cellularity of the bone marrow was normal. Her quantitative immunoglobulins, lymphocyte subsets, lymphocyte proliferation with mitogens (phytohemagglutinin and concanavalin A), neutrophil chemotaxis, CH_{50} and nitroblue tetrazolium (NBT) tests were all in normal limits. Cyclic neutropenia was diagnosed by monitoring her neutrophil count two or three

times a week during the frist six weeks following intial presentation. Neutrophil counts were regularly fluctuating with 21-23 day periodicity. neutrophils disappeared from the peripheral blood for three to five days and the patient developed upper and lower respiratory infections, aphthous gingivostomatitis, swelling of the lips and fever during the neutropenic periods. She was then put on prophylactic timethoprim-sulfamethoxazole therapy.

After the diagnosis the patient was followed-up by a local physician with an occasional visit to Hacettepe Children's Hospital (once in 2-3 years) for about ten years.

She was admitted again at 14.5 years of age with the complaints of fever and general malaise in addition to aggravation of the oral symptoms during the neutropenic periods which prevented her from attending school. We therefore started to treat the patient with intermittent subcutaneous rhG-CSF injections of 5 µg/kg/day, just before the initiation of mouth ulcers and/or other infection-related symptoms and signs. no side effects of rhG-CSF were reported and she showed a moderate response to G-CSF therapy clinically with no serious infections except gingivostomatitis of three weekly cycles.

After one year of rhG-CSF therapy, at 16 years of age, she was admitted with pretibial edema without arterial hypertension. Urine examination showed proteinuria when blood chemistry revealed renal function impairment characterized by hypoalbuminemia (total protein: 5.3 g/dl, albumin: 2.5 g/dl), increased serum creatinine (2.7 mg/dl) and decreased glomerular filtration rate (32.5 ml/min/1.73 m^2). Serum C3, C4, IgM and IgA levels were normal while IgG level was moderately decreased (412 mg/dl). Other cellular and humoral immunity tests were within normal limits. There was bilateral kidney enlargement with increased parenchymal echogeneity on abdominal ultrasonography. A renal needle biopsy revealed amyloidosis of AA type; on the suspicion of familial Mediterranean fever (FMF, Type II), colchicine therapy was started. Eight months after the start of the therapy, she still has proteinuria in nephrotic range with deteriorating renal function.

Discussion

Little is known about the pathogenesis of cyclic neutropenia. The cycling of netrophils is accompanied by cycling of other cellular elements, especially the monocytes, and monocyte cycles are opposite to neutrophil cycles, with low neutrophil counts being accompanied by high monocyte counts. The bone marrow exhibits a period of intense myelopoiesis after the period of neutropenia, suggesting the operation of a regulatory negative feed back loop[1]. A well defined etiology has not been established. Sequential bone marrow morphologic changes in patients with cyclic neutropenia and findings after bone marrow transplantation both in humans and in gray collie dogs are consistent with the presence of a defect in granulopoietic progenitor cells. Accumulating evidence indicates that the defect lies either in altered sensitivity of myeloid progenitor cells to growth factors or in defective regulation of granulopoiesis by accessory cells[1].

Until recently the dosage and administration scheme and therapeutic unitilty of rhG-CSF in children with cyclic neutropenia was not well characterized[2-5,7,8]. Most treatment modalities including splenectomy, hormone injections, corticosteroids, intravenous immunoglobulin therapy and nutritional supplements either failed or were marginally successful[1]. In 1989 Hammond et al.[8] reported a benefit with intermittent s.c. rhG-CSF in patients with cyclic neutropenia. The propensity for recurrent mucositis and infection was markedly attenuated. Occurrence of amyloidosis in patients with cyclic neutropenia is rare. As far as we know from a medline survey of 1970-1997, there are at least 270 patients with cyclic neutropenia but only three patients with cyclic neutropenia associated with amyloidosis[9,10]. All previousy reported patients with this combination suffered from frequent infections in association with an inadequate or lack of treatment with G-CSF. In addition, at the time of establishment of the diagnosis of renal amyloidosis, the patients had suffered for almost 20 years, and this is also in agreement with our patient's state. Recently, release of acute-phase serum amyloid-A protein (SAA) during repeated infections/inflammation is suggested to play a major role in the development of secondary amyloidosis, which was also shown in our patient. We suspected the presence of familial Mediterranean fever (FMF) in the presented case, which is commonly complicated by AA type amyloidosis showing renal involvement in untreated cases.

We, therefore, started colchicine therapy, although there was no family or patient history in accordance with FMF. Nevertheless, it cannot be excluded since the Turkish population is especially predisposed and in certain individuals and families amyloidosis is the first and sole clinical manifestation of FMF.

Although effective G-CSF therapy may delay the manifestation of amyloidosis, it can be anticipated that, as it lengthens the survival of the patients, the overall incidence of amyloidosis in cyclic neutropenia might even increase in the future, especially in patients with moderate response to G-CSF.

Unfortunately, it is not presently known why only a few of the patients with cyclic neutropenia are predisposed to develop amyloidosis. Thus it is not possible to recognize the patients at risk in advance. On the other hand, this may be related to the success of the treatment of cyclic neutropenia with G-CSF. To the contrary of that in human beings, in canine cyclic neutropenia there is a high incidence of the development of secondary amyloidosis[11]. This may support the idea that the mechanisms for amyloid deposition are different between human and animal species. Chronic immune activation in various primary immunodeficiencies may also lead to secondary amyloidosis[12,13], but this does not seem sufficient to explain amyloidosis in this case by itself, since the patient did not experience chronic or serious infections. Underlying FMF as another causative predisposing factor cannot be excluded unless a specific mutation in FMF gen is detected[14].

Our patient received G-CSF therapy without the appearance of any complications decribed in relation to its administration, which include exanthema, transient bone pains, arthralgias, arthritis, thrombocytopenia and anemia, leukocytoclastic vasculitis and leukocytoclastic vasculitis complicated by acute renal failure. However, secondary amyloidosis has been suspected to be related to the G-CSF usage in a patient with Felty's syndrome who developed renal AA amyloidosis after prolonged treatment with G-CSF[15].

Gastrointestinal symptoms such as diarrhea and intestinal obtruction were the presenting sings of amyloidosis in the previously described patients of cyclic neutropenia in contrast with the present case who presented with nephropathy[9,10]. This underscores the value of analyzing the urine and renal function in patients with cyclic neutropenia, as the discovery of proteinuria may be the first clue to amyloidosis.

We conclude that although amyloidosis papears to be extremely rare in cyclic neutropenia, it should be taken into account, and urine and renal function tests must be undertaken regularly, at least in cases who remained untreated for a long period of time or who demonstrate a moderate response to G-CSF.

REFERENCES

1. Bernini JC. Diagnosis and management of chronic neutropenia during childhood. Pediatr Clin North Am 1996; 43: 773-791.
2. Welte K, Zeidler C, Reiter A, et al. Differential effects of granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor in children with severe congenital neutropenia. Blood 1990; 75: 1056-1063.
3. Ishida Y, Higaki A, Tauchi H, Yokota Y, Matsuda H. Disappearance of neutrophil fluctuations in a child with cyclic neutropenia by combination therapy of granulocyte colony-stimulating factor and high dose immunoglobulin. Acta Paediatr Jpn 1995; 37: 388-390.
4. Jayabose S, Tugal O, Sandoval C, Li K. Recombinant human granulocyte colony stimulating factor in cyclic neutropenia: use of a new 3-day-a-week regimen. Am J Ped Hematol Oncol 1994; 16: 338-340.
5. Danielsson L, Harmenberg J. Intermittentt rG-CSF treatment in cyclic neutropenia. Eur J Haematol 1992; 48: 123-124.
6. Tınaztepe K. Renal amyloidosis in childhood: an overview of the topic with 25 years experience. Turk J Pediatr 1995; 37: 357-373.
7. Tsuda M, Urakami T, Watanabe S, et al. Recombinant human granulocyte colony-stimulating factor therapy for cyclic neutropenia associated with common variable immunodeficiency. Acta Paediatr Jpn 1993; 35: 124-126.
8. Hammond WP 4th, Price TH, Souza LM, Dale DC. Treatment of cyclic neutropenia with granulocyte colony-stimulating factor. N Engl J Med 1989; 320: 1306-1311.
9. Shiomura T, Ishida Y, Matsumoto N, Sasaki K, Ishihara T, Miwa S. A case of generalized amyloidosis associated with cyclic neutropenia. Blood 1979; 54: 628-635.
10. Lange RD, Crauder CG, Cruz P, et al. Cyclic neutropenia. A tale of two brothers and their family. Am J Pediatr Hematol Oncol 1981; 3: 127-133.
11. Machado EA, Gregory RS, Jones JB, Lange RD. The cyclic hematopoietic dog: a model for spontaneous secondary amyloidosis. A morphologic study. Am J Pathol 1978; 92: 23-34.
12. Öner A, Demircin G, Tınaztepe K, Pekuz O, Ersoy F. Hyperimmunoglobulin M syndrome associated with systemic amyloidosis type AA. Eur J Pediatr 1995; 154: 995.

13. Tezcan İ, Ersoy F, Sanal Ö, Gönç EN, Arıcı M, Berkel Aİ. A case of X-linked agammaglobulinemia presenting with systemic amyloidosis. Arch Dis Child 1998; (in press).

14. Babior B, Matzner Y, The familial mediterranean fever gene-cloned at last. N Engl J Med 1997; 337: 1548-1549.

15. Del pozo C, Sanchez L, Albero MD, Arenas MD. Prologed treatment with granulocyte colony-stimulating factor in a patient with Felty's syndrome and chronic renal failure from secondary amyloidosis. Nephrol Dial Transplant 1997; 12: 1727-1729.

Severe lymphopenia in tuberculosis

A mere coincidence or a significant association?

E. Nazlı Gönç[1], Seza Özen[1], Ayhan Göçmen[1], Yeşim Zafer[1], İlhan Tezcan[1]

[1]*Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey*

SUMMARY: Gönç EN, Özen S, Göçmen A, Zafer Y, Tezcan İ. Severe lymphopenia in tuberculosis: a mere coincidence or a significant association? Turk J Pediatr 2000; 42: 65-67.

A variety of infectious agents can cause secondary immunodeficient states. We herein present a one-year-old patient, admitted to the hospital with severe lymphopenia, who was subsequently diagnosed as tuberculosis. After the antituberculosis (anti TB) therapy was started, the clinical condition and the immunologic findings of the patient improved. We have thus concluded that the transient lymphopenia of the patient was due to Mycobacterium tuberculosis. We suggest that immunodeficiency should be investigated more often in children with tuberculosis and that further studies will shed light on the pathogenesis of this aspect of the disease.

Key words: childhood, lymphopenia, tuberculosis.

The altered immune status in infectious diseases has been an attractive subject for many clinicians. Quantitative and qualitative abnormalities in white blood cells have been clearly demonstrated in various infections; lymphopenia and certain immune deficient states have been associated with a number of infectious agents such as brucella[1], Epstein-Barr virus[2] cytomegalovirus[3,4], human immunodeficiency virus (HIV)[5] and even Mycobacterium tuberculosis. However, in most of these, the mechanism of secondary immunodeficiency induced by infectious agents has not yet been well established.

Tuberculosis is still a common disease not only in developing countries but also in developed countries, where a resurgence has occurred. We herein present an infant with tuberculosis who developed severe lymphopenia.

Case Report

A one-year-old girl was admitted to Hacettepe University Children's hospital with the symptoms of persistent gastroenteritis, lethargy and high fever. During the previous two months, she had not gained any weight. She had received two diphtheria-pertussis-tetanus (DPT) and oral polio vaccines but no BCG vaccine had been given. She was the fifth child of parents with second degree consanguinity. Her two brothers had died at four and eight months of age of unknown causes. The socioeconomic status of the family was very low.

On admission, she was in a septic state. Her weight and length were below the third percentile. She had severe dehydration, ascites and marked hepatosplenomegaly.

On laboratory examination, severe lymphopenia (total white blood cell count: 9000/mm^3, peripheral smear: 98% polymorphonuclear leukocyte, 2% lymphocyte; absolute lymphoyte count: 180/mm^3) was detected. the liver enzymes and bilirubin levels were elevated. She had deep metabolic acidosis. C reactive protein was positive. The antibodies against hepatitis A, B and C, cytomegalovirus, Epstein-Barr virus, HIV, and the titers of agglutinins for salmonella and brucella were all negative. No infectious agents were recovered from repeated nasopharyngeal, urine, stool, blood and bone marrow cultures. The sweat chloride concentration, the alpha^1 antitrypsin level, and the chest X-ray were normal. Abdominal ultrasonography showed ascites, hepatomegaly with marked parenchymal heterogeneity and splenomegaly. Bone marrow revealed lymphopenia.

The plasma immunoglobulin levels were normal; IgA: 101 mg/dl (25-158 mg/dl), IgG: 599 mg/dl (452-1192 mg/dl), IgM: 101 mg/dl (50-200 mg/dl). The delayed hypersensitivity skin tests for

candida, phytohemagglutinin and purified protein derivative were negative. Adenosine deaminase and purine necleoside phosphorylase levels were within normal limits. The serum isohemagglutinin titer anti A was 1/128 and the titers of antibodies for trivalent polio vaccine were as follows: T1: 1/32, T2: 1/32, T3: 1/128. On the other hand, the lymphoycte subpopulations CD3, CD4, CD8 and CD19 were extrmely low (Table I). In vitro lymphocyte proliferative responses to mitogens, phytohemagglutinin and concanavalin-A were normal.

Table I. Absolute Lymphocyte Count and Lymphocyte Subpopulations Detected on the Given Dates

Date	Absolute lymphoycte count	Lymphocyte subpopulations			
		CD3	CD4	CD8	CD19
At admission	180/mm^3	1%	1%	1%	0%
After 3 weeks	960/mm^3	81%	58%	32%	0%
After 4 weeks	2640/mm^3	88%	61%	29%	0%
After 5 weeks	2150/mm^3	79%	57%	29%	6%
After 7 weeks	2980/mm^3	33%	25%	14%	20%
After 9 weeks	5200/mm^3	32%	21%	16%	62%
After 3 months	3900/mm^3	41%	30%	14%	49%
After 6 months	4100/mm^3	58%	34%	24%	32%

The metabolic acidosis and severe dehydration were corrected in itially. Her general status deteriorated in the subsequent three days. Ciprofloxacin and amikacin were started empirically for her septic state. She was then diagnosed with tuberculosis by the twice positive polymerase chain reaction (PCR) for Mycobacterium tuberculosis in ascites fluid and a positive BCG test[6]. The direct examination of ascites fluid and gastric aspirates for acid-fast bacilli and the cultures were all negative. The chest X-ray of the patient's father revealed unilateral costophrenic sinus obliteration, raising the possibility of pulmonary tuberculosis. Intermittent antiTB therapy with isoniazid and rifampicin was started both for the patient and her father. A month later, the clinical condition of the patient improved and there was an increase in the absolute lymphocyte count (Table I). After six months of well-controlled treatment, she gained weight and improved markedly in motor and mental activity. The spleen was no longer palpable, the liver was reduced in size and ascites disappeared. After six months of treatment, the repeated PPD test revealed an induration of 15 mm in diameter.

Discussion

The incidence of tuberculosis has declined steadily over the past century due to impraved socioeconomic conditions in developed countries, but in recent years the disease became a common problem both in developed and developing countries despite widespread application of the BCG vaccination[7-9].

In tuberculosis, quantitative[10-15] and qualitative[16,17] abnormalities in both B cells and T cells have been reported in the literature; however, the most prominent abnormality is a CD4 lymphopenia and reversal of CD4/CD8 ratio[13,15]. There are only two reports of a relative B cell lymphopenia[13,18]. Our case is the first presentation of severe B and T cell depletion. After the initiation of the antiTB therapy, the first improvement was in the T cell count, although B lymphopenia persisted for seven weeks.

A primary immunodeficiency was ruled out by the improvement of clinical and laboratory parameters with antiTB therapy. The normal circulating amounts of immunoglobulins, despite decreased B cells in peripheral blood, may reflect the activation of B cell clones in lymphoid organs before the development of the secondary immune defect[19]. On the other hand, it may also be speculated that a defect in the lymphocyte migration from lymphoid organs to the circulation might have been responsible for the lack of these cells in the periphery[20]. An alternative possibility for the lack of lymphocytes in the circulation may be the sequestration of these cells in tuberculous granulomas as suggested by Onwubalili et al.[13]. Normal immunoglobulin and isohemagglutinin levels, good specific antibody response and normal in vitro lymphocyte proliferation tests of our patient were also suggestive of efficient lymphoyctes, although not detected in the periphery.

No other infectious agents were detected in this patient except Mycobacterium tuberculosis. Delacourt et al.[21] claimed that the PCR is the most specific and sensitive method for the diagnosis of mycobacterium tuberculosis, especially in childhood. Many data establish the utility of the PCR test for the rapid detection of Mycobacterium tuberculosis[22,23]. The BCG test, which was found to be positive in our patient, has been previously reported to have higher sensitivity and specificity than the PPD test in diagnosis of tuberculosis. The BCG test is unaffected by age, nutritional status, or by type and localization of infection[6]. The

diagnosis of tuberculosis was strengthened by the improvement of the clinical signs and symptoms as well as of the lymphopenia with antiTB therapy. We were unable to recover Mycobacterium tuberculosis by traditional culture methods because a combination of broad spectrum antibiotics which also cover Mycobacterium tuberculosis had to be administered for the patient's severe septic state before the evaluation of tuberculosis. The malnutrition might also have contributed to the immunodeficient state of this patient.

We conclude that the transient lymphopenia of this case was associated with Mycbacterium tuberculosis. The abnormal lymphocyte traffic might have been responsible for this condition. We suggest that immunodeficiency should be investigated more often in children with tuberculosis. Further studies will shed light on the pathogenesis of this aspect of the disease.

REFERENCES

1. al-Eissa-Y, al-Nasser M. Haematological manifestations of childhood brucellosis. Infection 1993; 21: 23-26.
2. Sullivan JL, Woda BA. Lymphoreticular responses to viral infections. In: Nathan DG, Oski FA (eds). Hematology of Infancy and Childhood (4th ed) Vol. 2. Philadelphia: W.B. Saunders Co; 1993: 1355-1356.
3. Carney WP, Hirsch MS. Mechanisms of immunosuppression in cytomegalovirus mononucleosis. II. Virus-monocyte interactions. J Infect Dis 1981; 144: 47-54.
4. Groshang T, Hrowitz S, Lovchik J, Davis A, Hong R. Chronic cytomegalovirus infection, immunodeficiency and monoclonal gammopathy-antigen driven malignancy? J Pediatr 1976; 88: 217-223.
5. Bofill M, Janossy G, Lee CA, Macdonald Burns D, et al. Laboratory control values for CD4 and CD8 T lymphoyctes. Implications for HIV-1 diagnosis. Clin Exp Immunol 1992; 88: 243-252.
6. Göçmen A, Kiper N, Ertan Ü, Kalaycı Ö, Özçelik U. Is the BCG test of diagnostic value in tuberculosis? Tubercle Lung Dis 1994; 75: 54-57.
7. Kochi A. The global tuberculosis situation and the new control strategy of the World Health Organization. Tubercle 1991; 72: 1-6.
8. Collins FM. Antituberculous immunity: new solutions to an old problem Rev Infect dis 1991; 13: 940-950.
9. Sudre P, ten Dam G, Kochi A. Tuberculosis: a global overview of the situation today. Bull World Health Organ WHO 1992; 70: 149-159.
10. Humber DP, Nsanzumuhire H, Aluoch JA, et al. Controlled double-blind study of the effect of rifampin on humoral and cellular immune responses in patients with pulmonary tuberculosis and in tuberculosis contacts. Am Rev Respir Dis 1980; 122: 425-436.
11. Katz P, Goldstein RA, Fauci AS. Immunoregulation in infection caused by Mycobacterium tuberculosis: the presence of suppressor monocytes and the alteration of subpopulations of T lymphocytes. J Infect Dis 1979; 14: 12.
12. Beck JS, Potts RC, Kardjito T, Grange JM. T4 lymphopenia in patients with active pulmonary tuberculosis. Clin Exp Immunol 1985; 60: 49-54.
13. Onwubalili JK, Edwards AJ, Palmer L. T4 lymphopenia in human tuberculosis. Tubercle 1987; 68: 195-200.
14. Turett GS, Telzak EE. Normalization of CD4+ T-lymphocyte depletion in patients without HIV infection treated for tuberculosis. Chest 1994; 105: 1335-1337.
15. Ashtekar MD, Samuel AM, Kadival GV, sakhalkar V, Rajadhyaksha S, Virdi SS. T lymphocytes in pulmonary tuberculosis. Indian J Med Res 1993; 97: 14-17.
16. Lenzinin L, Rottoli P, Rottoli L. The spectrum of human tuberculosis. Clin Exp Immunol 1977; 27: 230-237.
17. Uberoi S, Malaviya AN, Chattopadhyay C, Kumar R, Shrinivas. Secondary immunodeficiency in miliary tuberculosis. Clin Exp Immunol 1975; 22: 404-408.
18. Sestini P, Perari MG, Occhioni P. Lymphocyte subpopulations in tuberculosis after treatment with chemotherapy and thymostimulin. Int J Immunopharmacol 1985; 7: 618.
19. Keusch GT. Immunologic mechanisms in infectious diseases. In: Stiehm ER (ed). Immunologic Disorders in Infants and Children (4th ed). Philadelphia: W.B. Saunders Co; 1996: 956-974.
20. Westermann J, Pabst R. Lymphocyte subsets in the blood: a diagnostic window onthe lymphoid system? Immunol Today 1990; 11: 406-410.
21. Delacourt C, Poveda JD, Chureau C, et al. Use of polymerase chain reaction for improved diagnosis of tuberculosis in children. J Pediatr 1995; 126: 703-709.
22. Shah S, Miller A, Mastellone A, et al. Rapid diagnosis of tuberculosis in various biopsy and body fluid specimens by the amplicor Mycobacterium tuberculosis polymerase chain reaction test. Chest 1998; 113: 1190-1194.
23. Iinuma Y, Ichiyama S, Yamori S, et al. Diagnostic value of the amplicor PCR assay for initial diagnosis and assessment of treatment response for pulmonary tuberculosis. Microbiol Immunol 1998; 42: 281-287.

Allergic bronchopulmonary aspergillosis in two patients with cystic fibrosis

Deniz Anadol[1], Uğur Özçelik[1], Nural Kiper[1], Ayhan Göçmen[1]

[1]Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

SUMMARY: Anadol D, Özçelik U, Kiper N, Göçmen A. Allergic bronchopulmonary aspergillosis in two patients with cystic fibrosis. Turk J Pediatr 2000; 42: 68-71.

Allergic bronchopulmonary aspergillosis (ABPA) is hypersensitivity to Aspergillus fumigatus which manifests as episodic wheezing, usually refractory to bronchodilator therapy, with fixed and transient pulmonary infiltrates, central bronchiectasis, blood eosinophilia, elevated serum IgE level, immediate skin reactivity to an A. fumigatus antigen and precipitating antibodies to A. fumigatus. It is an unusual complication of asthma and cystic fibrosis (CF). We present two cystic fibrosis patients with ABPA treated successfully with prednisone and, in Case 1 also with itraconazole. The physician should be alert to the possibility of ABPA whenever CF patients present with the new infiltrates, high serum total IgE and other positive parameters of A. fumigatus sensitization. Treatment with systemic steroids should be started in order to prevent irreversible lung damage.

Key words: allergic bronchopulmonary aspergillosis, cystic fibrosis.

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitive reaction to Aspergillus fumigatus which was first described by Hinson et al. in 1952[1]. It is an unusual complication of asthma, cystic fibrosis (CF) and other bronchitic pulmonary diseases, and is a relatively uncommon pulmonary disease in childhood[2]. It manifests clinically as episodic wheezing, usually refractory to bronchodilator therapy. Its diagnostic features include fixed and transient infiltrates, central bronchiectasis, blood eosinophilia, elevated serum IgE level, immediate skin reactivity to an A. fumigatus antigen and precipitating antibodies to A. fumigatus[3]. Here, we report two cystic fibrosis patients with allergic bronchopulmonary aspergillosis.

Case Reports

Case 1

A seven-year-old boy who was the third child of nonconsanguineous parents was admitted to our hospital because of failure to thrive, chronic cough and recurrent sinusitis. On physical examination, his weight was 19.5 kg (< 5th percentile) and his height was 127 cm (10th percentile). Clubbing of the fingers, bilateral crackles and rhonchi on auscultation were prominent findings. Chest x-ray showed bilateral bronchiectatic changes and paracardiac infiltration (Fig. 1). Laboratory findings showed normal serum biochemical values, but the sputum culture revealed Staphylococcus aureus and Pseudomonas aeruginosa. As his sweat chloride concentration was 74 mEq/L, he was diagnosed with cystic fibrosis. He was delta F508 heterozygous in mutation analysis. His pulmonary function test revealed obstructive pattern unresponsive to bronchodilator as well as restrictive pattern on spirometry (VC: 50%, FVC: 49%, FEV1: 40%, FEV1/FVC: 75%, FEF25-75: 25%). He had an IgE level of 893 IU/ml in blood and positive A. fumigatus specific IgE and was therefore diagnosed with ABPA. He had no skin reactivity to A. fumigatus antigen. he was treated with intravenous antibiotics (ceftazidime, amikacin), inhaled tobramycin, pancreatic enzymes, multivitamins, inhaled human DNA'se and prednisone (1 mg/kg/day orally). The prednisone dose was tapered to 0.5 mg/kg on alternate days in four months as his clinical status improved. On his follow-up, the serum total IgE level was 2000 IU/ml, so the prednisone dose was increased to 1 mg/kg/alternate day, but as the IgE levels were

no longer decreasing, itraconazole was added to his therapy. His prednisone was tapered to 0.25 mg/kg/alternate day with this therapy. He has been taking prednisone for 22 months and itraconazole for 12 months; no side effects have been noted with this therapy to date.

Case 2

A 15-year-old boy whose parents were second cousins presented with chronic diarrhea when he was three years old and was diagnosed to have cystic fibrosis, as his sweat chloride concentration was 118 mEq/L. Staphylococcus aureus and Pseudomonas aeruginosa were cultured from his sputum. He was 621+1 G-T homozygous in mutation analysis. He was treated with pancreatic enzymes, multivitamins and antibiotics.

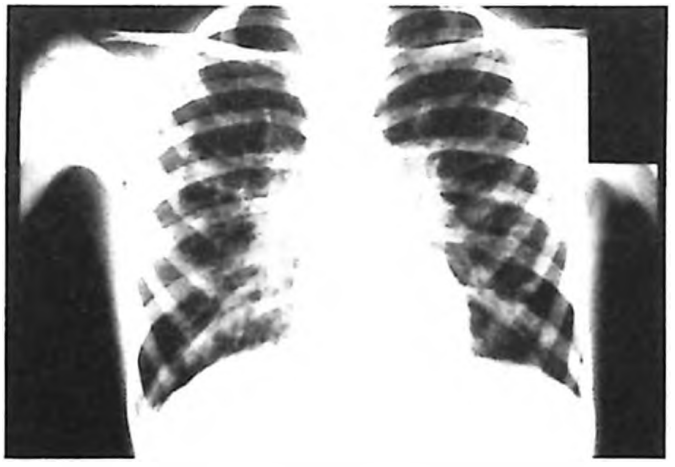


Fig. 1. Chest x-ray of Case 1 showing bilateral bronchiectatic changes and paracardiac infiltration.

When he was 13 years old, a lobectomy was performed for cystic bronchiectasis which was noticed at the right upper lobe in thoracal computerized tomography. On his clinical follow-up, at the age of 15, he complained of chronic productive cough, his chest x-rays revealed fixed infiltrates (Fig. 2) and pulmonary function tests revealed an obstructive pattern unresponsive to bronchodilator as well as a restrictive pattern on spirometry (VC. 54%, FVC: 49%, FEV1: 40%, FEV1/FVC: 75%, FEF25-75: 37%). He was diagnosed to have ABPA as his total blood IgE level was 2761 IU/ml and skin reactivity to A. fumigatus antigen was positive. Treatment with prednisone (1 mg/kg/day) was started. the prednisone dose was gradually tapered to 0.8 mg/kg/alternate day in five months and he is still being followed in our department.

Discussion

Allergic bronchopulmonary aspergillosis (ABPA) lung disease resulting from hypersensitivity induced in predisposed individuals by the ubiquitous fungus, Aspergillus fumigatus[4]. There is no clear consensus concerning the mechanisms of the lung disease in ABPA. However, it is apparent that both reaginic antibodies (IgE) and precipitating antibodies (IgG) are involved. An

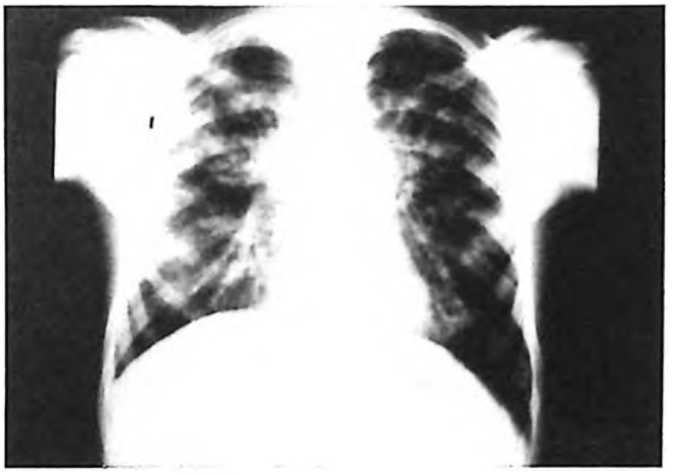


Fig. 2. Bilateral infiltrates and bronchiectatic changes in the chest x-ray of Case 2.

important component of the disease is persistent colonization of the airway with A. fumigatus and failure to clear the organism. That would explain the predilection of the disease for patients with asthma and cystic fibrosis (CF)[2]. This entity was documented as occurring in up to 22 percent of asthmatic patients in England[5] and in 9 percent in North America[6]. ABPA was reported in two patients with CF in 1965 by Mearns et al.[7]. It has since become a serious complication of CF but its prevalence is disputed, ranging from 0 to 11 percent, in the published literature[8-11].

Allergic bronchopulmonary aspergillosis (ABPA) is characterized by wheezing, which is usually unresponsive to bronchodilator therapy, and recurrent pneumonia[3]. Chest roentgenograms usually show homogeneous consolidation, bronchiectatic changes, contracted upper lobes with honeycomb lung, and branching shadows of mucus impaction with "tramline" shadows of thickened bronchial walls. The laboratory criteria for the diagnosis include sputum eosinophilia, peripheral blood eosinophilia, a positive immediate response to the skin prick test, a positive delayed reaction to intradermal testing, the presence of precipitating antibodies to A.

fumigatus, an increased serum IgE value and a positive specific reaction to A. fumigatus on an IgE antibody test (RAST)[2].

The diagnosis of ABPA in patients with CF is frequent overlooked because the signs and symptoms of each disease mimic each other. Therefore, with a high index of suspicion, the physician should be alert for ABPA in the presence of clinical and laboratory findings described above. Prick or intradermal skin testing with A. fumigatus antigen provides a screening test for ABPA, but confirmation requires other evidence of the disease[3]. An elevated level of total serum IgE is an important immunological finding in the diagnosis of ABPA in CF. A four-fold rise in total IgE, particularly to above 500 IU/ml, is strongly suggestive of the diagnosis of ABPA in children with CF[12]. The presence of high IgE and positive Aspergillus precipitins in conjunction with clinical deterioration and new radiological shadowing allow simplification of the diagnosis of ABPA in CF[12]. Both of our patients were suspected to have ABPA as they had persistent infiltrates and an obstructive pattern unresponsive to bronchodilator therapy on spirometry. Their elevated serum IgE led to the diagnosis, and specific IgE levels in Case 1 and positive skin test to A. fumigatus in Case 2 established the final diagnosis of ABPA.

The objective treatment fo ABPA in CF patients is to control acute exacerbation and to prevent lung damage. The first treatment choice is systemic corticosteroids; inhaled corticosteroids have been found to be ineffective[3]. Oral corticosteroids decrease the likelihood of permanent damage by suppressing the allergic response and inflammation associated with the colonization of A. fumigatus in the airways[13]. We aministered an initial dose of 1 mg/kg/day prednisone to both patients and reduced the dosage according to the clinical status of each. Corticosteroids usually produce a satisfactory clinical and immunologic response. However, such therapy is frequently associated with the well known long-term side effects of systemic corticosteroids. Itraconazole, a new orally administered azole antifungal agent of low toxicity, has an activity against Aspergillus spp. in vitro as well as in vivo. It has been shown to be useful in reducing corticosteroid requirements, reducing serum IgE concentrations and improving pulmonary functions in some patients with ABPA[13,14]. Treatment with prednisone was not so effective in our first case, so itraconazole was added to his therapy. With the administration of this drug, his IgE levels started to fall and the corticosteroid requirement was decreased. no side effects due to therapy were determined in the patient.

In conclusion, ABPA is a common complication of CF that may be difficult to identify. Its diagnosis requires a high index of suspicion. the physician should be alert to the possibility of ABPA whenever CF patients present with the new infiltrates, high serum total IgE and other positive parameters of A. fumigatus sensitization. Once the diagnosis is established, treatment with systemic steroids should be started in order to prevent irreversible lung damage. Patients should be followed-up for a long period, as relapses are seen, and a prolonged period of treatment is generally needed.

REFERENCES

1. Hinson KF, Moon AJ, Plummer NS. Bronchopulmonary aspergillosis-a review and a report of eight new cases. Thorax 1952; 7: 317-333.
2. Wilmott R, Kravitz RM. Allergic bronchopulmonary aspergillosis. In: Hilman BC (ed). Pediatric Respiratory Disease: Diagnosis and Treatment. Philadelphia: WB Saunders Co; 1993; 692-697.
3. Mroueh S, Spock A. Allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Chest 1994; 105: 32-36.
4. Greenberger PA, Patterson R. Allergic bronchopulmonary aspergillosis and the evaluation of the patient with asthma. J Allergy Clin Immunol 1988; 81: 646-650.
5. Henderson A, English M, Vecht J. Pulmonary aspergillosis. a survey of its occurrence in patients with chronic lung disease and a discussion of the significance of diagnostic tests. Thorax 1968; 23: 513-523.
6. Basich JE, Graves TS, Baz MN, et al. Allergic bronchopulmonary aspergillosis in corticosteroid dependent asthmatics. J Allergy Clin Immunol 1981; 68: 98-102.
7. Mearns M, Young W, Batten J. Transient pulmonary infiltrations in cystic fibrosis due to allergic aspergillosis. Thorax 1965; 20: 385-392.
8. Brueton MJ, Ormerod LP, Shah KJ, Anderson CM. Allergic bronchopulmonary aspergillosis complicating cystic fibrosis in childhood. Arch Dis Child 1980; 55: 348-353.
9. Maguire S, Moriarty P, Tempany E, Fitzgerald M. Unusual clustering of allergic bronchopulmonary aspergillosis in children with cystic fibrosis. Pediatrics 1988; 82: 835-839.
10. Simmonds EJ, Littlewood JM, Evans EG. Cystic fibrosis and allergic bronchopulmonary aspergillosis. Arch Dis Child 1990; 65: 507-511.

11. Carswell F, Hamilton A. Pathogenesis and management of aspergillosis in cystic fibrosis (letter). Arch Dis Child 1990; 65: 1288.

12. Marchant JL, Warner JO, Bush A. Rise in total IgE as an indicator of allergic bronchopulmonary aspergillosis in cystic fibrosis. Thorax 1994; 49: 1002-1005.

13. Nikaido Y, Nagata N, Yamamoto T, Yoshii C, Ohmori H, Kido M. A case of allergic bronchopulmonary aspergillosis successfully treated with itraconazole. Respiratory Medicine 1998; 92: 118-124.

14. Denning DW, Van Wye JE, Lewiston NJ, Stevens DA. Adjunctive therapy of allergic bronchopulmonary aspergillosis with itraconazole. Chest 1991; 100: 813-819.

Malignant fibrous histiocytoma in a child

A case report and review of the literature

Vedat Köseoğlu[1], A. Emin Kürekçi[1], Musta Kul[1], Haluk Öztürk[1], Ömer Günhan[1], Okan Özcan[1]

[1]*Department of Pediatrics, Gülhane Military Medical Academy, Ankara. Turkey*

SUMMARY: Köseoğlu V, Kürekçi AE, Kul M, Öztürk H, Günhan Ö, Özcan O. Malignant fibrous histiocytoma in a child: a case report and review of the literature. Turk J Pediatr 2000; 42: 72-75.

Malignant fibrous histiocytoma (MFH) is the most common soft tissue sarcoma of late adult file. It is extremely rare in children, though, and its existence in the pediatric population remains controversial. Although the most common site of tumor in children is the extremities, which is similar to findings of adults' series, different sites have been reported in children. Because of the rarity of this tumor in childhood, the approach to treatment of MFH is based primarily on the experience with adults.

We present the clinical and pathologic features of an eight-year-old boy with MFH located on his left retroperitoneum and also review the literature.

Key words: children, malignant fibrous histiocytoma, non-rhabdomyosarcoma soft tissue sarcoma.

Malignant fibrous histiocytoma (MFH) was first described as a distinct histological type of sarcoma in 1964, by O'Brien and Stout[1]. Although MFH is the most common soft tissue sarcoma of late adult life, it is extremely rare in children and its existence in the pediatric population remains controversial[2,3]. Several reports of large series note that three to 10 percent of all patients with MFH are less than 20 years old at the time of diagnosis and two to six percent of childhood soft tissue sarcomas have been reported as MFH[4,5]. Because MFHs are rare in children, the natural history of these tumors and prognostic factors that affect survival have not been well described[4].

We present the clinical and pathologic features of an eight-year-old boy with MFH located on his left retroperitoneum and also review the literature.

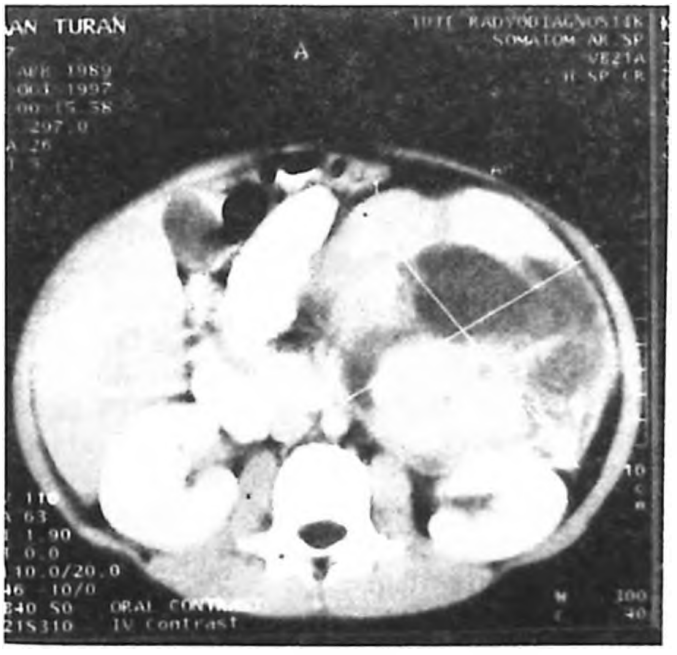
Case Report

An eight-year-old boy was admitted to our hospital with fever, fatigue, weight loss, palor, and painless upper left abdominal mass. Physical examination showed high fever (38.5 °C, axillary), pallor, and a painless left upper abdominal mass (diameter of 10x15 cm with irregular shape). The other physical findings were normal. Significant laboratory findings included decreased hemoglobin level (8.0 g/dl) and an elevated erythrocyte sedimentation rate (90 mm/h). Spot urine vanillylmandelic acid, alpha-fetoprotein, and β human chorionic gonadotropin levels were normal. The chest roentgenogram was also normal. Abdominal ultrasonography demonstrated a huge (8x20x12 cm) solitary lobulated echogenic mass with cystic areas located in the upper left abdomen. Its margins could not be seen clearly. Abdominal computed tomography showed a huge heterogeneous mass with cystic and necrotic areas located in the left hypochondrium and extending to the pelvis aperture (Fig. 1a). A surgical approach was undertaken but, owing to the size of the mass, complete excisional surgery could not be performed and only a partial excision was done. According to the postoperative staging system used in the Intergroup Rhabdomyosarcoma Studies, he was staged as a Group III disease[6]. Pathological examination revealed a solid tumor 8x10x5 cm with irregular contours infiltrating the pancreas. Histologically the tumor was highly cellular and consisted mainly of vacuolized atypical mesenchymal cells (Fig. 2). The mitotic rate was high, with more than 10 mitotic figures per 10 high power fields. Atypical mitotic figures were also seen. A wide necrosis was observe throughout the tumor. Immunohistochemical studies revealed the positivity of vimentin in the tumor tissue.

Although a rare positivity was found with S-100, immunohistochemical stains of NSE, chromogranine, CD-68, and desmin were found to be negative. He was diagnosed as having malignant fibrous histiocytoma based upon the clinical, laboratory and histopathological findings. Following surgery he was put on a combined chemotherapy consisting of vincristine (1.5 mg/m^2, day 1,8,15,22,43), ifosfamide (3 g/m^2, day 1,2,22,23,43,44) with mesna, cisplatinum (90 mg/m^2, day 3,24) and adriamycin (40 mg/m^2, day 43). After two courses of combined chemotherapy, he showed a good response to the treatment with more than 50 percent shrinkage of the tumor (Fig. 1b). It is planned that the will undergo a second operation for complete surgical removal of the residual tumor. After the operation, radiotherapy willbe given to the residual tumor.

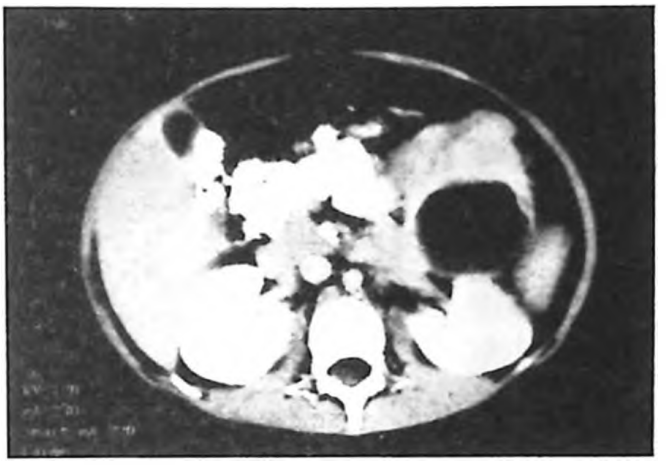
Discussion

Malignant fibrous histiocytoma is rare in childhood, and patients younger than 20 years of age have rarely been reported by investigators[4,5]. A male predominance has been noted in most pediatric series[4,5]. Although the most comon site of the tumor was the extremity, which is similar to findings of adults'



(a)

Fig. 1. The computed tomographic appearance of the tumor at the time of diagnosis (a) and after 2 cycles of chemotherapy (b).



(b)

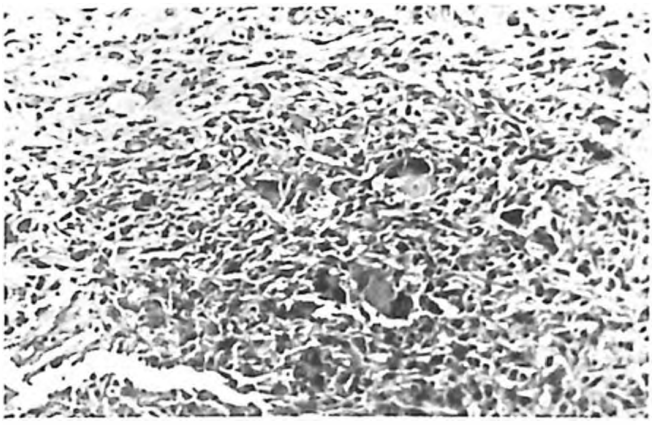


Fig. 2. Histological appearance of malignant fibrous histiocytoma consisting of pleomorphic neoplastic cells with some inflammatory response (H E x 200).

series, different sites have been reported in children[7-14]. Moreover, MFH is one of the most common radiation-induced sarcomas[4,15].

Cole et al.[5] reported that clinical presentation and physical findings of malignant fibrous histiocytoma are similar in children and adults. The diagnosis of MFH is made using histopathological and clinical findings. Berardo et al.[16] reported that although fine-needle aspiration in soft tissue lesions remains controversial, it is important in the initial triage of patients with soft tissue tumors, and is particularly accurate for confirming recurrent or metastatic disease. The tumors of MFH are solitary, multilobulated, fleshy masses that frequently involve deep muscle and are often larger than 5 cm at the time of diagnosis[5]. Most lesions occur as painless lumps in the extremities or retroperitoneum[5]. In our case, the lesion was painless and was located in left the patient's retroperitoneum.

Histological examination shows varying proportions of spindled fibroblastic-type cells and plumper histiocytic type cells lacking light microscopic features of differentiation other than collagen production. Some tumors contain a predominantly histiocytic pattern, others a predominantly fibroblastic pattern, and often there is a mixture of both patterns[5]. A number of histological subtypes are defined including storiform-pleomorphic, myxoid giant cell, inflammatory and angiomatoid. Immunohistochemical staining with alpha-1-antitrypsin, alpha-1-antichymotrypsin, and lysozyme, and ultrastructural features of myoblastic and histiocytic differentation suggest an origin of undifferentiated mesenchymal cells[5]. Pathological examination in our case showed that histopathology of the tumor was highly cellular and consisted mainly of vacuolized atypical mesenchymal cells. The mitotic rate was high, with more than 10 mitotic figures per 10 high power field. Atypical mitotic figures were also seen. A wide necrosis was observed throughout the tumor. Immonuhistochemical studies supported the diagnosis of MFH.

The most common site of metastasis is the lung, although metastases to the brain and other sites are also seen[5]. Local recurrence is common because the tumor often grows along fascial planes, forming a pseudocapsule that is often infiltrated[5]. Although lungs are the most common site of metastasis, primary MFH of the lungs has also been reported[9,11]. However, primary MFH of the lungs in children is extremely rare and frequently fatal[11].

Cytogenetic analysis of short-term cultures has revealed chromosomal abnormalities in MFH. The chromosome bands most frequently affected are 19p13, 11p11, 3p12, and 1q11[2,15]. It has been observed that tumors with 19p+ have a pronounced tendency to recur both locally and systemically[15]. Palmer et al.[3] demonstrated that cytogenetic and molecular genetic evidences of pediatric and adult MFHs are histologically related entities. Unfortunately, cytogenetic examination of the tumor tissue could not be done in our case.

Because of the rarity of this tumor in childhood, the approach to treatment of MFH is based primarily on the experience with adults[15]. Surgery is the mainstay of therapy, but there is a high rate of local recurrence even with wide local excision or amputation[5]. Because there is a low incidence of lymph node metastasis, lymph node resection is not recommended with the initial resection[5]. Although complete surgical excision remains the most effective therapy for MFH, several investigators have discussed the role of adjuvant chemotherapy and radiation therapy[4]. Zagars et al.[17] reported that patients with myxoid tumors do not require systemic therapy. Patients with nonmyxoid disease exceeding 5 cm are at significant risk for metastases, and the development of effective adjuvant treatment is an important research tool. Chemotherapy with vincristine, dactinomycin, and cyclophosphamide with or without doxorubicin has produced objective tumor regressions in children with advanced disease[15]. A study in adults suggests that ifosfamide may be a more effective agent against soft tissue sarcomas than cyclophosphamide[15]. Further, studies in adult patients with advanced disease have demonstrated a higher response rate after ifosfamide was added to the regimen. For this reason, we put our patient on a combined chemotherapy regimen consisting of vincristine, adriamycin and ifosfamide. The treatment of angiomatoid MFH is different from that for classic adult-type MFH. Because the risk of metastasis is very low, adjuvant chemotherapy is not indicated. However, this tumor does ocasionally metastasize. Radiation therapy with moderate doses (4000-6000 rad) has been shown to improve survival in various soft tissue sarcomas and substantially reduced the recurence rate in adults with MFH[5]. radiation therapy may be used in cases of an initially inoperable tumor or in patients in whom incomplete resection cannot be avoided[4].

Relatively few studies have examined the prognostic factors associated with MFH. According to the "Pediatric Oncology Group Non-Rhabdomyosarcoma Soft Tissue Sarcoma" grading system, angiomatoid MFH is classified as a low-grade (grade 1) tumor, and the remandier of MFH are intermediate or high-grade (grade 2) tumors. The survival rate of children with MFH described was somewhat better than that of several series of adult patients[4]. Corpron et al.[4] demonstrated that large tumor size (diameter > 5 cm) is predictive of a poorer prognosis. Tumor size has also been found to be a significant prognostic factor for adults with MFH[4].

Although MFH is rare in childhood, it should be kept in mind in the differential diagnosis of a child presenting with painless abdominal mass.

REFERENCES

1. O'Brien JE, Stout AP. Malignant fibrous xanthomas. Cancer 1964; 17: 1445-1455.
2. Iwasaki H, Isayama T, Ohjimi Y, et al. Malignant fibrous histiocytoma. A tumor of facultative histiocytes showing mesenchymal differentiation in cultured cell lines. Cancer 1992; 69: 437-447.
3. Palmer JL, Masui S, Pritchard S, Kalousek DK, Sorensen PH. Cytogenetic and molecular genetic analysis of a pediatric pleomorphic sarcoma reveals similarities to adult malignant fibrous histiocytoma. Cancer Genet Cytogenet 1997; 95: 141-147.
4. Corpon CA, Black CT, Raney RB, Pollock RE, Lally KP, Andrassy RJ. Malignant fibrous histiocytoma in children. J Pediatr Surg 1996; 31: 1080-1083.
5. Cole CH, Magee JF, Gianoulis M, Rogers PC. Malignant fibrous histiocytoma in childhood. Cancer 1993; 71: 4077-4083.
6. Maurer HM, Moon T, Donaldson M, et al. The Intergroup Rhabdmyosarcoma Study: a preliminary report. Cancer 1977; 40: 2015-2026.
7. Dillon P, Maurer H, Jenkins J, et al. A prospective study of nonrhabdomyosarcoma soft tissue sarcomas in the pediatric age group. J Pediatr Surg 1992; 27: 241-244; discussion 244-245.
8. Hari JK, AzzarelliB, Caldemeyer KS. Malignant fibrous histiocytoma in a 9-year-old girl. Pediatr Neurosurg 1996; 24: 160-165.
9. Nistal M, Jemenez-Heffeman JA, Hardisson D, Vguer JM, Bueno J, Garcia-Miguel P. Malignant fibrous histiocytoma of the lung in a child. An unusual neoplasm that can mimick inflammatory pseudotumor. Eur J Ped 1997; 156: 107-109.
10. Martinez-Salazar A, Supler M, Rojiani AM. Primary intracerebral malignant fibrous histiocytoma: immunohistochemical findings and etiopathogenetic considerations. Mod Pathol 1997; 10: 149-154.
11. Shah SJ, Craver RD, Yu LC: Primary malignant fibrous histiocytoma of the lung in a child: a case report and review of literature. Pediatr Hematol Oncol 1996; 13: 531-538.
12. Kim OH, Lee KY. Malignant fibrous histiocytoma of primary omental origin in an infant. Pediatr Radiol 1994; 24: 285-287.
13. Huang Z, Wei K. Malignant fibrous histiocytoma of the ascending colon in a child [letter]. Am J Gastroenterol 1993; 88: 972-973.
14. İlhan I, Arıkan U, Büyükpamukçu M. Rothmund-Thomson syndrome and malignant fibrous histiocytoma: a case report. Pediatr Hematol Oncol 1995; 12: 103-105.
15. Miser JS, Triche TJ, Kinsella TJ, Pritchard DJ. Other soft tissue sarcomas of chidhood. In: Pizzo PA, Poplack DG (eds). Principles and Practice of Pediatric Oncology (3rd ed). Philadelphia, New York: Lippincott-Raven Press; 1997: 865-888.
16. Berardo MD, Powers CN, Wakely PE Jr, Almeida MO, Frable WJ. Fine-needle aspiration cytopathology of malignant fibrous hstiocytoma. Cancer 1997; 81: 228-237.
17. Zagars GK, Mullen JR, Pollack A. Malignant fibrous histiocytoma: outcome and prognostic factors following conservation surgery and radiotherapy. Int J Radiat Oncol Biol Phys 1996; 34: 983-994.

Partial splenic embolization in beta - thalassemia major

A case report

Adalet Meral[1], Betül Sevinir[1], Yurtkuran Sadıkoğlu[2], Ergun Nacarküçük[1], Ünsal Günay[1]

[1]Departments of Pediatrics, and [2]Department of Radiology, Uludağ University Faculty of Medicine, Bursa, Turkey

SUMMARY: Meral A, Sevinir B, Sadıkoğlu Y, Nacarküçük E, Günay Ü. Partial splenic embolization inbeta-thalassemia major: a case report. Turk J Pediatr 2000; 42: 76-79.

Partial splenic arterial embolization was performed in a thalassemic child for hypersplenism manifested by splenomegaly, leukopenia, thrombocytopenia, and anemia requiring frequent erythrocyte transfusion. During a follow-up period of 11 months, his hematological parameters improved significantly and the spleen size decreased. Partial splenic embolization could be an alternative therapy to surgical splenectomy for thalassemic children with hypersplenism.

Key words: splenic embolization, thalassemia.

Thalassemia is considered to be the most common genetic disorder world-wide. It occurs in a high frequency in a broad region from the Mediterranean through Asia. Good transfusion programs may retard the development of splenomegaly. There is usually increasing hypersplenism and physical discomfort because of the grossly enlarged spleen. Progressive splenic sequestration of transfused cells is observed by 1-8 years of age. Splenic trapping of platelets, leukocytes and erythrocytes produces thrombocytopenia, leukopenia, anemia and an increased transfusion requirement which accelerates iron loading. The spleen is removed when the red cell transfusion requirement exceeds 200-250 ml packed red cell/kg/year[1].

Surgical anatomy may be distorted secondary to enlarged spleen and dissection can be difficult in massive splenomegaly. Additionally, thrombocytopenia increases the hemorhagic risk during surgery. Therefore, surgical removal of the spleen may carry a significant mortality and morbidity[2]. Laparoscopic splenectomy, which is often used in congenital spherocytosis or idiopathic thrombocytopenia, may also be difficult to perform due to increased collaterals and spleen size[3]. For this reason, partial splenic embolization (PSE) has been accepted as an alternative procedure to splenectomy in patients with splenomegaly is performed in children with beta-thalassemia major as will as with other diseases causing hypersplenism[4-6].

Case Report

A 17-year-old boy had been followed for beta-thalassemia major since he was six months old. A splenectomy could not be performed until 1993 when the patient was 13 years old because of the family's disagreement on the matter. In 1993, the surgical procedure was not successful due to massive splenomegaly with distorted collaterals. PSE was planned three years later when he developed severe pancytopenia and his transfusion requirement increased to six units of erythrocyte infusion per month. Before PSE, he developed local hyperemia and enduration in the periumbilical region. Subcutaneous abscess formation was determined by ultrasonography. The drainage of the abscess material revealed Escherichia coli and Klebsiella pneumonia, which were treated with a combination of penicillin, clindamycin and amikacin. He responded to treatment in 20 days and there was no further growth in the cultures.

He was vaccinated with 23 valent pneumococcal polysaccharide vaccine (Pasteur Merieux^{R}) and Hamophilus influenzae vaccine (Pasteur Merieux^{R}) before embolization. Penicillin (200,000 U/kg/day) and amikacin (15 mg/kg/day) intravenously were given 24 hours before the procedure and the following seven days. The procedure was performed under sterile conditions and intravenous sedation and local anesthesia were used.

A preliminary aortogram to view the celiac axis was obtained by approaching the femoral artery with a

5F catheter. A selective splenic arteriography was then performed (Fig. 1). The catheter was repositioned in the main splenic artery to determine its exact configuration and its branches. Controlled embolization of the peripheral splenic branches. Controlled embolization of the peripheral splenic branches and main splenic artery was performed using particles measuring 200 μ (IVALON^{R}). A postembolization arteriogram was obtained to show the occluded splenic artery (Fig. 2). Although the splenic artery seemed to be fully occluded by angiography, computerized tomography (CT) of the same region documented that the collaterals from the diaphragm and lumbar arterias flowed into the splenic parenchyma. The embolized splenic parenchyma was seen as hypodense regions by CT (Figs. 3, 4). It was determined that approximately 40 percent of the spleen was infarcted.

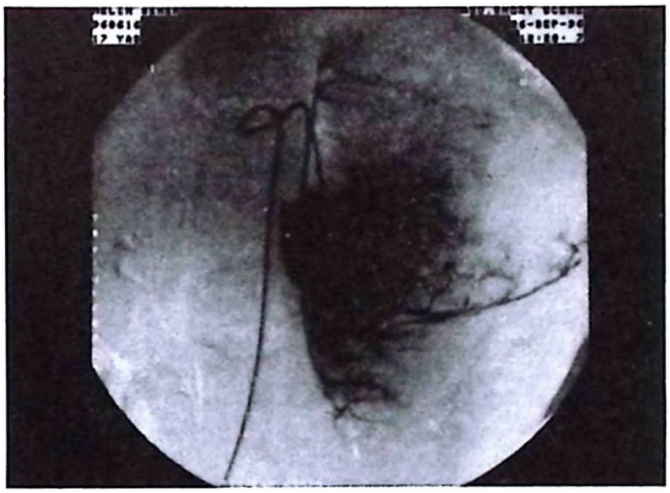


Fig. 1. Splenic arterial angiography before splenic embolization.

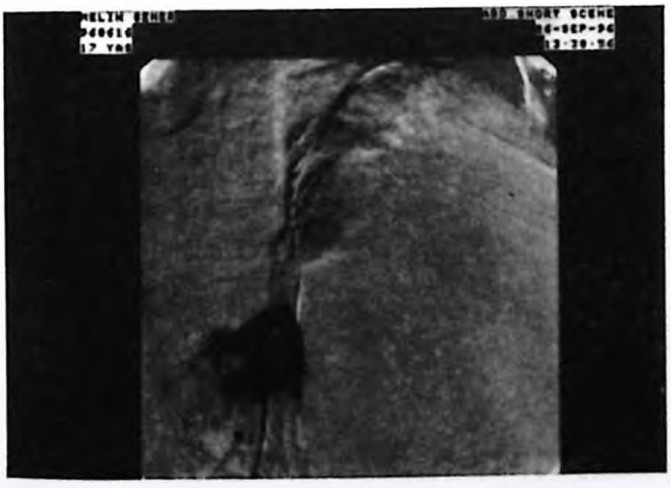


Fig. 2. Postsplenic embolization.

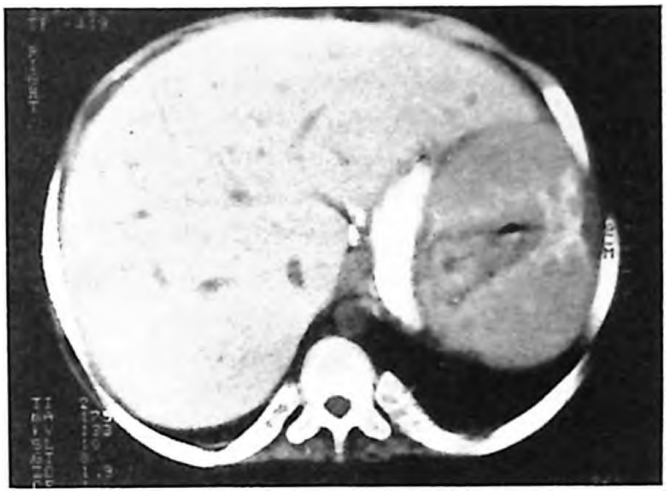


Fig. 3. Abdominal computed tomography showing the normal and necrotic splenic parenchyma.

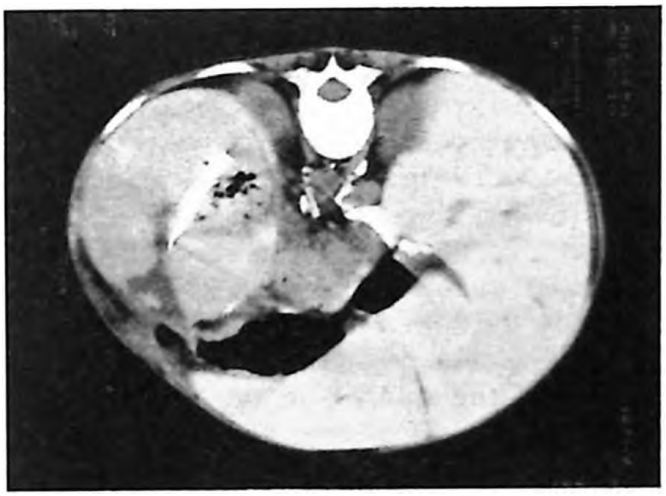


Fig. 4. Abdominal computed tomography showing the normal and necrotic splenic parenchyma.

Postoperative hemorrhage from the incision scar of the previous abscess occurred 48 hours after the embolization. It was attributed to the increased pressure in the collaterals following PSE. Somatostatin was thus administered to decrease the enhanced pressure of the splenic arterial bed. Active hemorrhage stopped after 72 hours of this treatment. However, serohemorrhagic and necrotic material continued to drain from the same region. It was determined by contrast radiography that this material was coming from the infarcted splenic parenchyma. A catheter was placed into the cavity. Irrigation with normal saline four times a day was performed through the catheter. Imipenem and tobramycin were started since Enterobacter boumani was grown in the cultures taken from the catheter.

Both leukocyte and thrombocyte counts increased during the first month of embolization. Necrotic drainage through the catheter ceased three months after PSE. Computed tomography controls demonstrated that the cavity size decreased from 9 cm to 4 cm. Antibiotherapy was discontinued since there was no further growth in the cultures.

Six months later, the spleen size decreased from 14 cm to 10 cm, determined by physical examination and ultrasonography, transfusion requirement decreased from 6 units to 2 units of erythrocyte infusions, and leukocyte (4,600-6,400/mm^3) and platelet counts (150,000-180,000/mm^3) both increased. The patient was lost due to severe myocardial dysfunction 11 months after PSE. During that period, his blood counts were stable as described above.

Discussion

Partial splenic embolization is accepted as a safe and effective procedure to surgical splenectomy for children with hypersplenism[6,7]. Hematological parameters improve for a long period of time and the spleen size decreases as a result of an infarction of greater than 40 percent of splenic mass[8]. However, the spleen size does not decrease to normal even after an infarction of more than 80 percent of the spleen[9]. In the present case, approximately 40 percent of the spleen was infarcted and thrombocyte and leukocyte counts increased two weeks after the procedure. Five months later, the increase of hematological parameters and decrease in transfusion requirement suggested that the PSE was successful.

The most important complications of PSE have been reported to be pleural effusion, pneumonia and spleen abscess[6]. In the present case, necrotic material drained from the infarcted region through the fistula connected to the previous periumbilical abscess cavity. The periumbilical abscess that developed before the procedure could be due to impairment of chemotaxis and netrophil migration, which may partially account for the increased susceptibility to infection in such children[10,11]. No serious infection following PSE was observed. The noninfarcted spleen might still continue to provide immunologic functions preventing the occurrence of overwhelming infections[12]. The hospitalization period was longer than expected due to prolonged resolution of the necrotic region. However, computed tomography in the third month after PSE showed that the resolution and organization of the infarcted region was completed.

Although repeat embolization is recommended in the literature for patients with a subnormal platelet count in whom the infarcted region has been less than 80 percent, our patient did not require a second procedure after eleven months of follow-up[6-9].

The patient died of severe myocardial infarction 11 months after PSE. This was due to previous increased transfusions which caused excess iron loading. However, during eleven months of follow-up, he had a better life quality since transfusion frequency decreased and he had no thrmbocytopenic complication. This outcome was achieved by 40 percent infarction of the splenic mass by arterial embolization.

Therefore, we believe that the morbidity and mortality associated with surgical splenectomy could be avoided using PSE in apropriate pediatric cases.

REFERENCES

1. Lukens JN. The thalassemias and related disorders: quantitative disorders of hemoglobin synthesis. In: Lee RG, Bithell TC, Foersterr J, Athens JW, Lukens JN (eds). Wintrobe's Clinical Hematology (9th ed) Vol. 1. London: Lea and Febiger; 1993: 1102-1145.
2. Schiller M. The spleen. In: O'Neill JA, rove MI, Grosfeld JL, Fonkalsrud WE, Coran AG (eds). Pediatric Surgery (5th ed) Vol. 2. St. Louis: Mosby; 1998: 1545-1554.
3. Tulman S, Holcomb GW 3d, Karamanoukian HL, et al. Pediatric laparoscopic splenectomy. J Pediatr Surg 1993; 28: 689-692.
4. Stanley P, Shen TC. Partial embolization of the spleen in patients with thalassemia. J Vasc Interv Radiol 1995; 6: 137-142.
5. Pinca A, Di Palme A, Soriani S, et al. Effectiveness of partial splenic embolization as treatment for hypersplenism in thalassemia major: a 7 year follow up. Eur J Haematol 1992; 49: 49-52.
6. Shah R, Mahour GH, Ford EG, Stanley P. Partial splenic embolization. An effective alternative to splenectomy for hypersplenism. Am Surg 1990; 56: 774-777.
7. Muguerza R, Lasseletta L, Vazquez J, et al. Partial splenic embolization in the treatment of hypersplenism. Long term results. Cir Pediatr 1995; 8: 11-16.
8. Brandt CT, Rothbarth LJ, Kumpe D, et al. Splenic embolization in children. long term efficacy. J Pediatr Surg 1989; 24: 642-645.

9. Watanabe Y, Todani T, Noda KT. Changes in splenic volume after partial splenic embolization in children. J Pediatr Surg 1996; 31: 241-244.
10. Matzner Y, Goldfarb A, Abrahamov A, et al. Impaired neutrophil chemotaxis in patients with thalassemia major. Br J Haematol 1993; 85: 153-158.
11. Kütükçüler N, Kutlu O, Nişli G, et al. Assessment of neutrophil chemotaxis and random migration in children with thalassemia major. Pediatr Hematol Oncol 1996; 13. 239-245.
12. Israel DM, Hassall E. Partial splenic embolization in children with hypersplenism. J Pediatr 1994; 124: 95-100.

Postoperative graft thrombosis in Fontan procedure

Ali Sarıgül[1], Bora Farsak[1], İsmail Koramaz[1], Mustafa Tok[1], Yurdakul Yurdakul[1]

[1]*Department of Thoracic and Cardiovascular Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey*

SUMMARY: Sarıgül A, Farsak B, Koramaz İ, Tok M, Yurdakul Y. Postoperative graft thrombosis in Fontan procedure. Turk J Pediatr 2000; 42: 80-83.

Fontan reparir could be used as the definitive palliation in many forms of complex cyanotic congenital heart disease. But thrombosis can occur after a modified Fontan operation (right atrium-right ventricular connection with a conduit). Appropriate management of this complication includes thrombolytic therapy, thrombectomy and revision (if surgically remediable causes of the thrombosis are identified) or redo operation.

Two repair operations were performed for the treatment of thrombosis of the right side of the heart in paitents in whom we had previously performed Bjork modification (right atrium-right ventricular connection with a conduit). The thromboses occurred 6 and 9 years after the operation, respectively. In both cases, the redo Fontan operation was successfully performed using a dacron tube graft. Patients were anticoagulated after the operation. Risk of thrombosis of the right side of the heart after the Fontan repair may be minimized with the use of prophylactic anticoagulation in high-risk patients soon after the operation.

Key words: Fontan procedure, graft thrombosis, redo Fontan procedure.

Since its first introduction by Fontan and Baudet, the Fontan repair is considered the definitive palliation for patients with many forms of complex cyanotic congenital heart disease[1-3].

However, enthusiasm for and success with the one ventricle repair have been limited by our inability to prevent or adequately treat complications, such as recurrence of serous effusions, protein-losing enteropathy and thrombosis of the right side of the heart[4-11]. In this article, we address the issue of neointima formation and thrombosis in two patients, which resulted in inadequate flow through the graft between the right atrium and right ventricle, and two successful redo Fontan operations. We also review previously reported cases so as to better understand this rare but catastrophic complication.

Case Reports

Case 1

A 3.5-year-old girl was admitted to our children's hospital in 1983 for the first time with the complaints of cyanosis, fatigue and clubbing.

Her angiography revealed a large atrial septal defect, tricuspid hypoplasia, pulmonary arteriovenous fistula and hypoplastic right ventricle, and with this diagnosis it was decided the patient was a candidate for the Fontan procedure.

A modified Fontan procedure was performed on February 25, 1985 using a standard means of cardiopulmonary by-pass with a 24 mm Meadox-dacron graft (Meadox Medicals, Inc., oakland, NJ, USA).

There were no postoperative complications, and after an uneventful 15 days she was discharged with dipyridamole, digoxin, spironolactone and furosemide.

With he exception of a right bundle branch block (RBBB), her postoperative periodic controls were in normal limits till 1994, when she admitted with fatigue and edema. Complete atrioventricular (A-V) block was diagnosed and an epicardial lead and pacemaker were implanted. But her complaints did not subside, and five months later she came to the emergency unit with cyanosis, edema and ascites. Echocardiogram showed narrowing of the graft with an elevated right ventricular pressure and 10 mmHg gradient inside the baffle. The next day she was taken into surgery for a redo Fontan operation.

The redo Fontan operation was performed with right atrial-femoral cannulation and moderate hypothermia (26 °C), and a 24 mm Meadox-

dacron graft was implanted for atrio-ventricular connection (Fig. 1). The old graft material had been narrowed by neointimal proliferation and thrombus formation (Fig. 2).

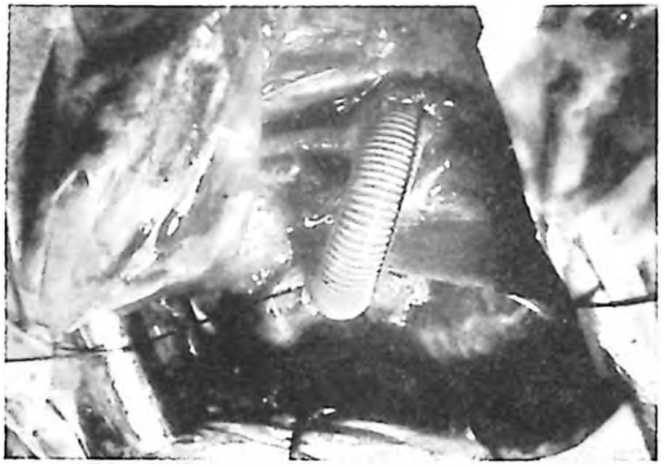


Fig. 1. Atrio-pulmonary connection with a 24 mm dacron graft at the end of the redo Fontan operation.

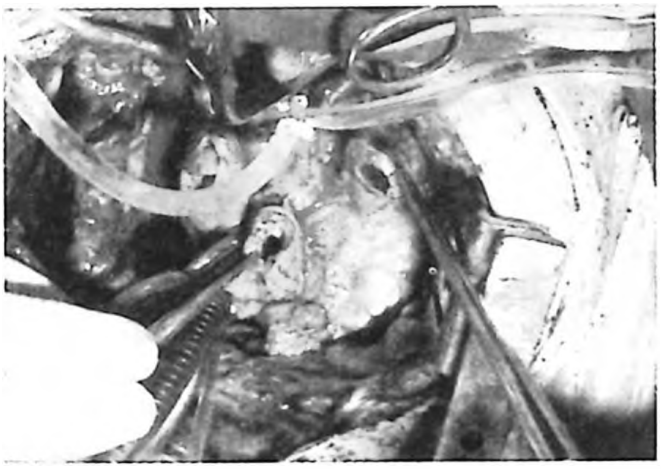


Fig. 2. The old graft material, which had been narrowed by the neointimal proliferation and thrombus formation.

Before hospital discharge, a control echocardiogram demonstrated patency in the graft. During her postoperative stay in hospital a protein-losing enteropathy was detected and a high protein diet was ordered (rich in protein and medium chain fatty acids). After an uneventful three weeks she was discharged. She is now free of symptoms, taking digoxin, spironolactone, and warfarin sodium, 38 months after her redo Fontan operation.

Case 2

A three-year-old boy was admitted to hospital in 1986 with cyanosis, at which time he was diagnosed with tricuspid atresia, atrial septum defect (ASD) and ventricular septum defect (VSD). With this diagnosis, a left Blalock-Taussig shunt was performed (1986).

Three years later a modified Fontan procedure was performed, and an atrio-ventricular connection was constructed using a 20 mm Meadox-dacron graft (Meadox Medicals, inc., Ocakland, NJ. USA).

After a symptom-free period of six years, he was admitted to hospital with congestive heart failure, ascites and edema. It was learned that his symptoms began four months previously and increased throughout this period.

Echocardiogram revealed narrowing of the graft, and angiography confirmed the diagnosis with an 8 mmHg gradient inside the baffle.

He was taken into surgery and a redo Fontan procedure was performed (using a 24 mm Meadox-dacron graft (Meadox Medicals, Inc., Oakland, NJ, USA) for the atriopulmonary connection. The old graft material had been narrowed by neointima and thrombus formation.

He was discharged after three weeks with warfarin sodium, digoxin he is having periodic controls and is symptom free.

Discussion

Right-sided thrombosis is a rare but fatal complication when it occurs after the Fontan procedure. In a review of the literature, we could not find many previously reported cases, and in the available clinical data, both in surgical and non-surgical interventions, the results are not satisfactory[4-13].

The data revealed that thrombosis may occur soon after the operation or may manifest itself several years after the Fontan repair (range 1 day to 15 years)[4-13].

Several factors have been implicated in predisposing a patient to thrombosis of the right side of the heart. Most of these can be grouped according to Virchow's triad of (1) stasis (2) abnormal mural surface and (3) increased viscosity or coagulability.

Systemic venous stasis may occur as a result of partial obstructions due to technical error, gradual narrowing of the anastomosis due to scarring, increased pulmonary arteriolar resistance[15,16], low cardiac output, enlarged redundant right atrium, heart block and other arrhythmias[5,15,16] or abdominal compression caused by ascites. In our patients, thrombosis

occurred after nine and six years, respectively. Although we did not observe any technical error, there was heart block and consequently ascites in one patient. Unfortunately, neither case was given anticoagulants after the first operation.

The patch or graft material used in the repair may inadvertently provide an abnormal mural surface. Central lines and shunts may provide a thrombogenic surface, which promotes thrombosis and should be removed as early as possible postoperatively. Increased blood viscosity may also contribute to formation of thrombi, as well as intravascular volume depletion and polycythemia.

Abnormalities of coagulation factors and proteins C and S and antithrombin III deficiency may develop and to formation of thrombi after the Fontan operation[7].

Diagnosis of a thrombus on the right side of the heart may be difficult. Echocardiography should be used in the routine surveillance of patients after the Fontan repair. Angiography should be performed if the diagnosis is suspected, thrombosis is unclear[4,7] or if the patient fails to make satisfactory progress after the operation. Because of the risk of embolus that may originate from the catheter tip, some groups advocate thoracal computerized tomography[18].

The best therapeutic option for acute thrombosis is unclear in the early postoperative period. If a remediable cause for the thrombosis is identified, operative intervention with thrombectomy and revision seems to be the most appropriate treatment.

Thrombolysis can be a logical alternative but it should probably be attempted only in patients who admitted early with acute thrombus formation, whose conditions are stable, who have no cantraindication for thrombolytic therapy or in whom reoperation would entail a prohibitively high risk[4].

Neither of our patients were good candidates for thrombolytic therapy as they presented with chronic symptoms.

In the early postoperative period heparinization followed by administration of warfarin may be the safest therapy currently available[5,7]. Therapeutic use fo aspirin and dipyridamole in this context has been reported only once and in that case it did not prevent recurrent thrombosis[9]. Some authors have recommended routine prophylactic anticoagulation with warfarin[5,6,13].

After the first operation, our patients were prescribed antiaggregant agents which did not preclude the thrombus formation. They were anticoagulated with warfarin sodium after the redo operations.

In our cases, we preferred performing a redo Fontan operation using a new graft material. We did not prefer thrombectomy in view of the formation of an irregular-surfaced thick neointima in both cases which might be a hazard for new thrombus formation[14].

When a patient presents with congestive heart failure, cyanosis or fatigue after asuccessful Fontan operation, one must always keep in mind the graft thrombosis and the neointima formation and should advocate an aggressive approach to diagnois: echocardiography and, if not satisfactory, cardiac catheterization. Treatment should not only emphasize removal of the thrombosis, but also should address those factors that contributed to formation of the thrombus. warfarin anticoagulation should be used prophylactically in patients who are at a high risk for thrombosis of the right side of the heart.

REFERENCES

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971; 26: 240-248.
2. Dajee H, Deutsch LS, Benson LN, Perloff JK, Laks H. Thrombolytic therapy for superior vena caval thrombosis following superior vena cava-pulmonaray artery anastomosis. Ann Thorac Surg 1984; 38: 637-639.
3. DeLeon SY, Koopot R, Mair DD, et al. Surgical management of occluded conduits after the Fontan operation in patients with Glenn shunts. J Thorac Cardiovasc Surg 1984; 88: 601-605.
4. Dobell AR, TruslerGA, Smallhorn JF, Willarcs WG. Atrial thrombi after the Fontan operation. Ann Thorac Surg 1986; 42: 664-667.
5. Downing TP, Danielson GK, Ritter DG, Jlusrud PR, Seward JB. Pulmonary artery thrombosis associated with anomalous pulmonary venous connection: an unusual complicatilon following the modified Fontan procedure. J Thorac Cardiovasc Surg 1985; 90: 441-443.
6. Fontan F, Deville C, Quaegebeur J, et al. Repair of tricuspid atresia in 100 patients. J Thorac Cardiovasc Surg 1983; 85: 647-660.
7. Juaneda E, Haworth SG. Pulmonary vascular structure in patients dying after a Fontan procedure. The lung as a risk factor. Br Heart J 1984; 52: 575-580.

8. Laks H, Milliken JC, Perloff JK, et al. Experience with the Fontan procedure. J Thorac Cardiovasc Surg 1984; 88: 939-951.
9. Mahony L, Nikaidoh H, Fixler DE. Thrombolytic treatment with streptokinase for late intraatrial thrombosis after modified Fontan procedure. Am J Cardiol 1988; 62: 343-344.
10. Matsuda H, Kawashima Y, Takano H, Miyamoto K, Mori T. Experimental evaluation of atrial function in right atrium-pulmonary artery conduit operation for tricuspid atresia. J Thorac Cardiovasc Surg 1981; 81: 762-767.
11. Okita Y, Miki S, Kusuhara K, et al. Massive systemic venous thrombosis after Fkontan operation. report of a case. Thorac Cardiovasc Surg 1988; 36: 234-236.
12. Hedrick M, Elkins RC, Knott-Craig CJ, Razook JD. Successful thrombectomy for thrombosis of the right side of the heart after Fontan operation. J Thorac Cardiovasc Surg 1993; 105: 297-301.
13. Anagnostopulos CE, Connery CP, Bilfinger TV, et al. Initial clinical experience with rectus sheath grafts in congenital heart defects. J Cardiovasc Surg 1995; 36: 429-432.
14. Shannon FL, Campbell DN, Clarke DR. Right atrial thrombosis: rare complication of the modified Fontan procedure. Pediatr Cardiol 1986; 7: 209-212.
15. Sharratt GP, Lacson AG, Cornel G, Virmani S. Echocardiography of intracardiac filling defects in infants and children. Pediatr Cardiol 1986; 7: 189-194.
16. Cromme-Dijkhuis AH, Henkens CM, Bijleveld CM, Hillege HL, Bom VJ, vander Meer J. Coagulation factor abnormalities: possible thrombotic risk factors after Fontan operations. Lancet 1990; 336: 1087-1090.
17. Tamaki S, Takagi Y, Mizuno S, et al. A case report of redo Fontan operation. Nippon Kyobu Geka Gakkai Zasshi 1993; 41: 1390-1393.

Inguinoscrotal hematocele of the newborn

Aydın Şencan[1], İrfan Karaca[1], Arzu Bostancı Şencan[1], Erol Mir[1]
[1]Department of Pediatric Surgery, Dr. Behçet Uz Children's Hospital, İzmir, Turkey

SUMMARY: Şencan A, Karaca İ, Şencan AB, Mir E. Inguinoscrotal hematocele of the newborn. Turk J Pediatr 2000; 42: 84-86.

Neonatal inguinoscrotal hematocele is a very rare disease of the first few days of life. The cause of this pathology is thought to be related with the umbilical plastic clamp, with an incorrect clamping technique or with the infant's lying over the clamp. Surgical treatment is not necessary as long as testicular torsion is excluded. In this report, three cases of inguinoscrotal hematocele diagnosed at surgical exploration in our clinic are reported and the literature reviewed.

Key words: inguinoscrotal hematocele, hematoma, newborn.

Inguinoscrotal hematocele of the newborn is a very rare disease of the first few days of life[1,2]. The cause of this pathology is thought to be related with the umbilical plastic clamp or with an incorrect clamping technique, in which the clamp is either eccentric or too distal[3]. Other causes of acute scrotum should also be suspected in differential diagnosis. We present three cases of inguinoscrotal hematocele which were diagnosed between 1997 and 1998.

Case Reports

Case 1

Case 1 was a white male who was delivered vaginally at the 35th gestational week with a birth weight of 2500 g. There was no history of birth trauma. He was admitted to our clinic on the 1st postpartum day with symptoms of inguinoscrotal swelling and redness. On physical examination, redness and swelling of the right inguinoscrotal region were detected and an umbilical plastic clamp was present. The coagulation tests (platelet count, clotting and prothrombin time) were normal. The diagnosis of testicular torsion was suspected. On Doppler ultrasonography (USG), there was no blood flow in the right testis. At scrotal exploration it was observed that the testicular sheaths (dartos fascia and tunica vaginalis) were infiltrated by blood, but the testis was found inside the hematoma without evidence of torsion (Fig. 1). The hematoma was evacuated. Four days later the swelling had subsided, and the remainder of the hematoma in the inguinoscrotal skin had completely resolved by the end of the 8th day.

Case 2

Case 2 was a white male who was delivered vaginally at the 37th gestational week with a birth weight of 2800 g. There was no history of birth trauma. He was admitted to our clinic on the 3rd postpartum day with symptoms of right inguinoscrotal swelling and discoloration. On physical examination, redness, ecchymosis and swelling of the right inguinoscrotal region were detected and an umbilical plastic clamp was present. Coagulation tests were normal. The diagnosis of testicular torsion could not be excluded. On inguinoscrotal USG, intestinal segments were observed, but a Doppler examination could not be performed. The diagnosis of strangulated inguinal hernia was suspected. At inguinal exploration, hemorrhagic infiltration of the subcutis that extended to the homolateral scrotum was observed. Inguinal hernia was not present. The testicular sheaths were infiltrated by blood, but the testis was found inside the hematoma without evidence of torsion. The hematoma was evacuated. Three days later the swelling of the scrotum had subsided and the remainder of the hematoma in the inguinoscrotal skin had completely resolved by the end of the 7th day.

Case 3

Case 3 was a white male who was delivered vaginally at the 40th gestational week with a birth weight of 4200 g. There was no history of

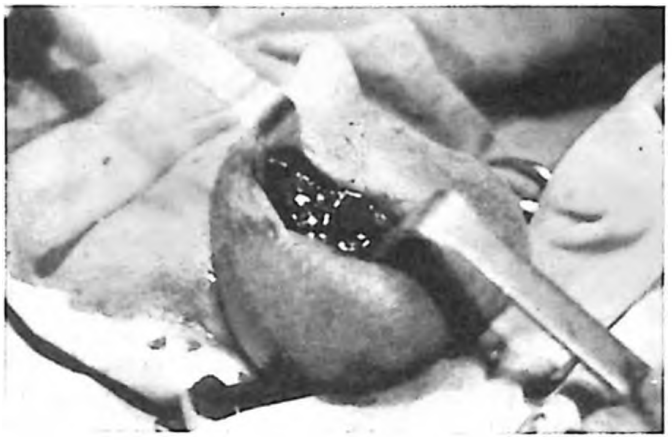


Fig. 1. Preoperative inguinoscrotal view of the first case.

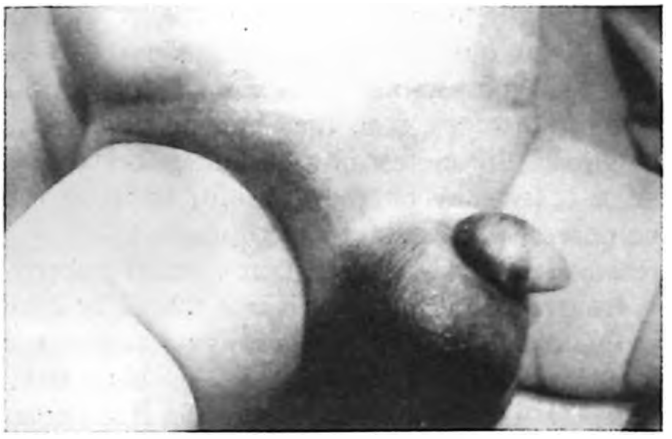


Fig. 2. Preoperative inguinoscrotal view of the third case.

birth trauma. He was admitted to our clinic on the 4th postpartum day with symptoms of right inguinoscrotal swelling and discoloration (Fig. 2). On physical examination, redness, ecchymosis and swelling of the right inguinoscrotal region were detected and an umbilical plastic clamp was present. The coagulation tests were normal. Blood flow in the right testis was determined on Doppler USG, but as testicular torsion could not be excluded by physical examination, he was explored via inguinal approach. The testicular sheaths were infiltrated by blood, but the testis was found inside the hematoma without evidence of torsion. The hematoma was evacuated. Two days later the swelling of the scrotum had subsided and the remainder of the hematoma in the inguinoscrotal skin had completely resolved by the end of the 7th day.

Discussion

Inguinoscrotal hematocele seen after delivery is thought to be due to compression by the umbilical clamp of the superficial inguinal vasculature (scrotal branches of the femoral or saphenous vein) or to an incorrect clamping technique, in which the clamp is either eccentric or too distal. Rupture of these vessels produces an inguinal hematoma, and consequent drainage to the homolateral scrotal area causes the scrotal hematoma. If the infant is in a prone position, the umbilical clamp makes a compression on the inguinal region which leads to the rupture of the superficial branches of the femoral vein[3,4]. In all three cases, as there was no history of birth trauma and as all the infants with normal coagulation tests had umbilical plastic clamps, the etiology of the inguinoscrotal hematocele could be explained by the same mechanism. Treatment of newborn hematocele may be conservative but surgical exploration is needed whenever the diagnosis is equivocal, since torsion of the testis may lead to testicular loss. In the first case, because Doppler USG did not show any blood flow, the diagnosis of testicular torsion could not be excluded and he was explored by scrotal approach. In the second case, the differential diagnosis of incarcerated hernia could not be made by physical examination and he was explored after an intestinal segment was determined on USG. In the third case, while blood flow of the right testis was determined on Doppler USG, exploration was performed because physical examination findings strongly suggested the diagnosis of testicular torsion. In all three cases, inguinoscrotal hematocele with no testicular torsion was observed at exploration. The differential diagnosis between inguinoscrotal hematocele and neonatal testicular torsion, appendicular testis torsion, idiopathic scrotal swelling, epididymo-orchitis, incarcerated hernia and Henoch-Schönlein purpura should be made. Epididymitis tends to occur with urinary tract symptoms, such as frequency, dysuria, fever, and pyuria, and it is seen more rarely in the neonatal period. Incarcerated hernia occurs as an irreducible mass in the inguinoscrotal region. Inguinoscrotal USG may show intestinal segments. Idiopathic scrotal swelling and Henoch-Schönlein purpura are rare pathologies causing acute scrotum. Neonatal testicular

torsion is often detected as a painless mass on initial post-delivery examination. The scrotal skin may be discolored ecchymotic, or edematous, as seen in inguinoscrotal hematocele. Doppler USG and radioisotope scan may help in differential diagnosis. In adolescents beyond pubertal age, such tests may be more useful because the volume of the testis is large enough to allow a reasonably high level of accuracy. Before puberty, however, when the testis is less than 1 or 2 ml in volume, such tests are of lower accuracy and have limited clinical usefulness. For this reason, differential diagnosis may be difficult. If testicular torsion is strongly ruled out and the diagnosis of inguinoscrotal hematocele is clearly apparent, non-operative treatment is suggested, but if there is even slight suspicion of testicular torsion, surgical exploration must be performed[5,6].

It is concluded that newborn hematocele is a benign, self-resolving condition that should always be considered when scrotal swelling and discoloration appear in the first few days of life. Surgical exploration is indicated when the differential diagnosis cannot be made. Otherwise, non-operative treatment is sufficient. For the prevention of this pathology, umbilical plastic clamps should be placed correctly and of infants with umbilical clamps should be positioned more carefully so as not to cause compression of the inguinoscrotal region.

REFERENCES

1. Klauber GT, Sant GR. Disorders of male external genitalia. In: Kelalis P, King L, Belman B (eds). Clinical Pediatric Urology. Philadelphia: WB Saunders; 1985: 878-858.
2. Rodríguez DD, Rodríguez WC, Rivera JJ, et al. Doppler ultrasound versus testicular scanning in the evaluation of acute scrotum. J Urol 1981; 125: 343-346.
3. Miliaras EV, Koutsoumis G, Miliaras D, Manios S. Neonatal inguinoscrotal hematocele. Pediatr Surg Int 1996; 11: 505-506.
4. Rodríguez-Alarcon J, Vargas LM, Solaun MR. Neonatal inguinoscrotal lesion produced by plastic umbilical clamp. J Pediatr 1978; 93: 1024-1025.
5. Noseworthy J. Testicular torsion. In: Ashcraft KW, Holder TM (eds). Pediatric Surgery (2nd ed). Philadelphia, Pennsylvania: WB Saunders; 1993: 595-601.
6. Hutson JM. Undescended testis, torsion, and varicocele. In: O'Neill JA, Rowe MI, Grosfeld JL, Fonkalsrud EW, Coran AG (eds). Pediatric Surgery (5th ed). St. Louis: Mosby-Year Book, Inc; 1998: 1087-1109.

A rare coexistence of two gastric outlet obstructive lesions: infantile hypertrophic pyloric stenosis and organoaxial gastric volvulus

Pelin Oğuzkurt[1], M. Emin Şenocak[1], Akgün Hiçsönmez[1]

[1]*Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey*

SUMMARY: Oğuzkurt P, Şenocak ME, Hiçsönmez A. A rare coexistence of two gastric outlet obstructive lesions: infantile hypertrophic pyloric stenosis and organoaxial gastric volvulus. Turk J Pediatr 2000; 42: 87-89.

Infantile pyloric stenosis is one of the most common conditions requiring surgery during the first few weeks of life. The association of infantile pyloric stenosis with gastric volvulus in an extremely uncommon occurrence. A 10-month-old male infant operated for infantile pyloric stenosis at two months of age is presented. His current problem was recurrent pulmonary infections and he was diagnosed to have organoaxial gastric volvulus and gastroesophageal reflux. The common features of presentation, radiological findings, surgical procedures and possible mechanisms of gastric volvulus associated with infantile pyloric stenosis are discussed.

Key words: gastric volvulus, infantile hypertrophic pyloric stenosis, gastric outlet obstructions.

The association of infantile pyloric stenosis (IPS) with other gastrointestinal tract anomalies is rarely encountered[1,2]. The uncommon association of IPS and gastric volvulus is not throughly mentioned in the literature. Gastric volvulus (GV), mesenteroaxial or organoaxial, is a rare condition in infancy and childhood[3,4]. It is known that conditions such as mental retardation with aerophagia, gastric outlet obstruction and tracheo-esophageal fistula, which result in gastric distention, may predispose to gastric volvulus[4,5]. It may occasionally be associated with diaphragmatic hernia or eventration, congenital bands and disorders causing gastric distension, and deficient gastric attachments as well as asplenia, or it may be idiopathic[6-9]. The association of two obstructive upper gastrointestinal disorders and late presentation of organoaxial volvulus after relief of infantile pyloric stenosis are discussed in this report.

Case Report

A 10-month-old male infant was hospitalized with symptoms of fever, cough, grunting respirations, and intercostal and subcostal retractions. He had had several attacks of pneumonia over the previous four months with clinical pictures milder than with the current attack. His past history revealed an operation for IPS at the age of two months. During Ramstedt's pyloromyotomy, duodenal perforation was noticed and was primarily sutured. The postoperative period was uneventful and he had been discharged on the 8th postoperative day. He was in good health until the time of his first severe pneumonia attack at six months of age. Chest examination revealed fine rales in both lungs. The physical examination of the abdomen revealed a supraumbilical right transverse incision and epigastric distention. Routine laboratory tests including complete blood count, urinalysis and blood chemistry were within normal limits. The sweat chloride test and quantitative immunoglobulins A, M, G were normal. The posteroanterior chest X-ray revealed interstitial pneumonia and right paracardiac infiltration with a distended stomach with double superimposed air-fluid level (Fig. 1). While the technetium-99m sulphur colloid scan revealed

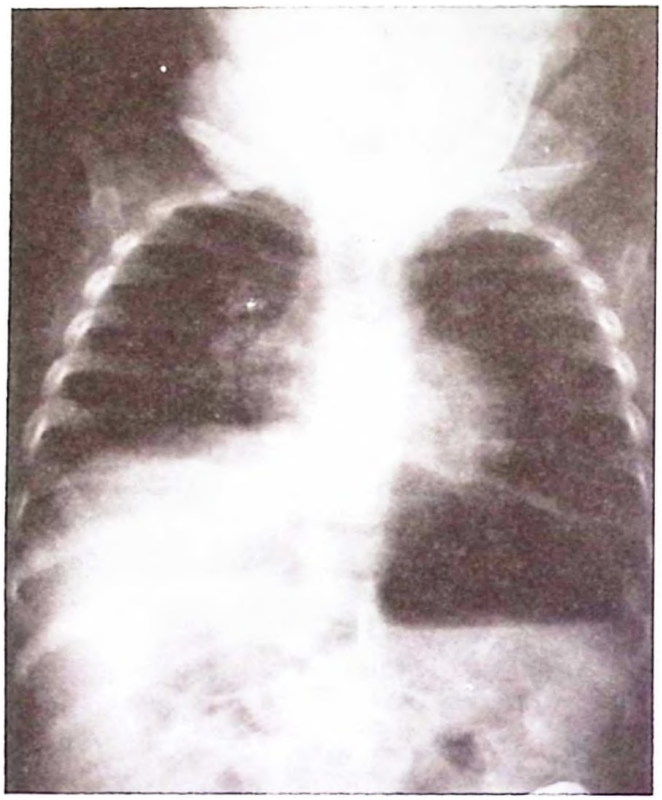


Fig. 1. Configuration of the distended stomach and double superimposed air-fluid levels suggestive of upside down stomach on plain erect X-ray consistent with organoaxial gastric volvulus.

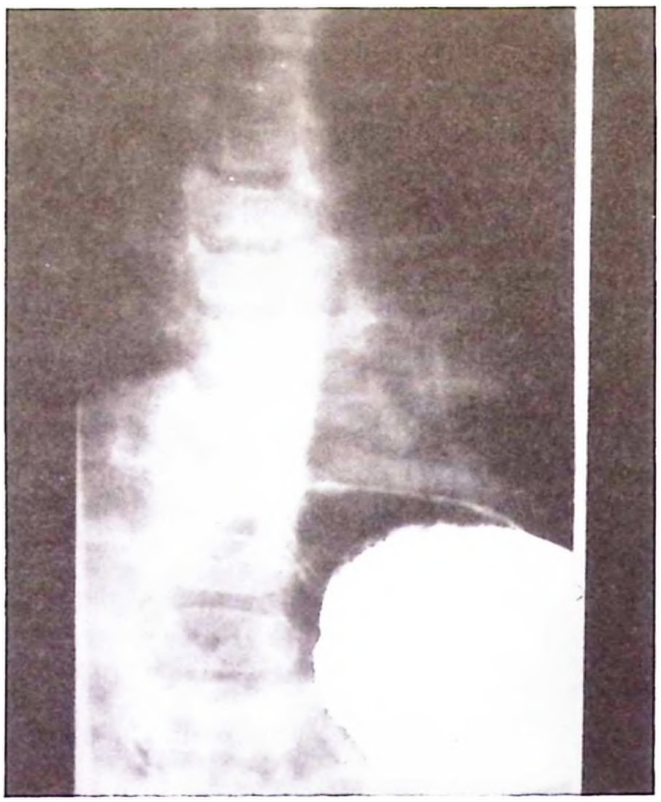


Fig. 2. Upper gastrointestinal series confirms the presence of organoaxial gastric volvulus associated with gastroesophageal reflux.

grade 2 gastroesophageal reflux, the barium swallow revealed both gastroesophageal reflux and organoaxial gastric volvulus (Fig. 2). After 15 days of antibiotic treatment, he underwent surgery. The greater curvature of the stomach was free and was located below the diaphragm under the left lobe of the liver. No adhesive bands due to the previous operation were identified. The greater curvature of the stomach was reduced and anterior gastropexy was performed with 3/0 nonabsorbable interrupted sutures. The postoperative period was uneventful and the patient was discharged on the 7th postoperative day. The barium swallow, performed 15 days after the operation, was normal. During six months follow-up, the patient did not have symptoms of gastroesophageal reflux disease and had no respiratory infections.

Discussion

Infantile pyloric stenosis, one of the most common conditions requiring abdominal surgery during infancy, may be rarely associated with other alimentary tract anomalies[1,10]. In large series, the malformations mentioned are esophageal atresia, malrotation, Meckel's diverticulum, diaphragmatic hernia, Hirschsprung's disease and exomphalos[1]. The occurrence of GV has not been previously mentioned among the associated alimentary tract anomalies in IPS.

Gastric volvulus, which is defined as an abnormal degree of rotation of one part of the stomach around another, is a rather uncommon condition in children[11]. The stomach is securely held in place by gastrophrenic ligaments and esophageal hiatus, the retroperitoneal fixation of the duodenum, the short gastric vessels and the gastrocolic ligament[12]. For a volvulus to occur, these ligaments must be absent or stretched[4]. It is reported that gastric distention may also predispose to GV[3,4]. Although ulceration or tumors causing gastric outlet obstruction may result in gastric volvulus in adults[4], in children GV may occur in mentally retarded and aerophagic patients[5], as well as in patients with tracheoesophageal fistula (TEF),

both of which result in gastric distention[4]. According to the clinical course, GV is classified as acute or chronic. It has been reported that no identifiable anomaly has been detected in 33.3 percent of the cases with chronic gastric volvulus[7].

Gastric volvulus may cause nonspecific symptoms such as epigastric distention and episodic vomiting or retching, or chronic aspiration symptoms due to gastroesophageal reflux which was successfully treated with conservative measures without any need for fundoplication[11]. Localized distention of stomach and horizontal position with a single air fluid level or double superimposed air-fluid levels may be seen[5]. It may even be missed in barium swallow showing the lower position of the esophagogastric junction and distortion of the antrum and duodenum[5].

In our clinic, 116 patients were diagnosed as IPS between December 1989 and December 1996. In this series, the associated alimentary tract anomalies were H-type TEF in one case, Hirschsprung's disease in one case and duodenal web in the second part of the duodenum in another case. The only operative complication was duodenal perforation which was recognized during the operation and primarily sutured. The postoperative complications in this series were two cases of eventration.

Organoaxial gastric volvulus was not recognized as an associated malformation or postoperative complication in our series nor in the large series in the literature[1]. In the presented case, organoaxial gastric volvulus was probably present when the patient was operated for IPS. An upper gastrointestinal series was not performed preoperatively because of the greater curvature of the stomach during the operation. Our patient presented with the complications of chronic GV such as gastroesophageal reflux and pneumonia at 10 months of age, but no responsible anomaly was identified.

Hypertrophic pylorus in association with gastric volvulus was reported in a newborn who was found to have a distended stomach and hypertrophied pylorus at laparotomy for organoaxial gastric volvulus; both gastropexy and pyloroplasty were performed[5]. Therefore, IPS causing gastric distention may be a predisposing factor for the occurrence of gastric volvulus. Khemani et al.[13] reported organoaxial gastric volvulus following vagotomy and pyloroplasty for chronic gastric outlet obstruction, and attributed the pathology to the laxity of the gastric suspensory ligaments and postoperative adhesions. This may explain the late presentation of organoaxial gastric volvulus after gastric decompression due to the relief of gastric outlet obstruction[13].

The presented case represents and idiopathic form of GV with chronic symptoms which manifest at a later age probably after subclinic attacks of mild vomiting or gastroesophageal reflux disease. It is therefore suggested that the presented case represents a coexistence of two obstructive upper gastrointestinal pathologies.

REFERENCES

1. Ahmed S. Infantile hypertrophic pyloric stenosis associated with major anomalies of the alimentary tract. J Pediatr Surg 1970; 5: 660-666.
2. Zenn MR, Redo SF. Hypertrophic pyloric stenosis in the newborn. J Pediatr Surg 1993; 28: 1577-1578.
3. El-Gohary MA, Etiaby A. Gastric volvulus infants and children. Pediatr Surg Int 1994; 9: 486-488.
4. Ziprkowski MN, Teele RL. Gastric volvulus in childhood. AJR 1979; 132: 921-925.
5. Cameron AE, Howard ER. Gastric volvulus in childhood. J Pediatr Surg 1987; 22: 944-947.
6. Aoyoma K, Tateishi K. Gastric volvulus in three children with asplenic syndrome. J Pediatr Surg 1986; 21: 307-310.
7. Dudgeon DL. Lesions of the stomach. In: Ashcraft KW, Holder TM (eds). Pediatric Surgery (2nd ed). Philadelphia: W.B. Saunders Company; 1993: 295-297.
8. Rowe MI, O'Neill JA Jr, Grosfeld JL. *Essentials of Pediatric Surgery*. St Louis: Mosby Company; 1995: 504-505.
9. Şenocak ME, Büyükpamukçu N, Hiçsönmez A. Chronic gastric volvulus in children: a 10 year experience. Z Kinderchir 1990; 45: 159-163.
10. Bell MJ. Infantile pyloric stenosis: experience with 305 cases at Louisville Children's Hospital. Surgery 1968; 64: 983-989.
11. Samuel B, Burge DM, Griffiths DM. Gastric volvulus and associated gastro-oesophageal reflux. Arch Dis Child 1995; 73: 462-464.
12. Scherer LR. Peptic ulcer and other conditions of the stomach. In: O'Neill JA, Rowe MI, Grosfeld JL, Fonkalsrud EW, Coran AG (eds). Pediatric Surgery (5th ed). St Louis: Mosby; 1998: 1127-1128.
13. Khemani R, Kantheria C, Shah P. Organoaxial volvulus of the stomach following corrective surgery for gastric outlet obstruction. Indian J Gastroenterol 1992; 11: 144.

TRIBUTE TO REVIEWERS FOR VOLUME 41

Our journal depends on reviewers for their generous donations of time, effort and expertise. We thank them for their great contribution to maintaning the journal's high standards.

AKALAN Nejat, MD
AKOVA Murat, MD
AKYÜZ Canan, MD
ALTAY Çiğdem, MD
ANLAR Banu, MD
ARIYÜREK Macit, MD
ARSLAN Serap, MD
ATAKAN Nilgün, MD
BAKKALOĞLU Ayşın, MD
BALKANCI Ferhun, MD
BAŞARAN Nurettin, PhD
BEREKET Abdullah, MD
BERKEL İzzet, MD
BERKMAN Erdoğan, MD
BEŞBAŞ Nesrin, MD
BÖKESOY Işık, MD
CEYHAN Mehmet, MD
COŞKUN Turgay, MD
ÇAĞLAR Melda, MD
ÇELİKER Alpay, MD
ÇETİN Mualla, MD
ÇİFTÇİ Arbay Özden, MD
DEMİRCİN Metin, MD
DİNÇER Fitnat, MD
DOĞAN Rıza, MD
ECEVİT Zafer, MD
ERDEM Gülşen, MD
ERDENER Uğur, MD
GÖĞÜŞ Safiye, MD
GÖKLER Bahar, MD
GÖKŞİN Eflatun, MD
GÜMRÜK Fatma, MD
GÜR Deniz, PhD
GÜRAKAN Figen, MD
GÜRGEY Aytemiz, MD
GÜRSEL Türkiz, MD
HALİLOĞLU Mithat, MD
HİÇSÖNMEZ Gönül, MD
KALYONCU Fuat, MD
KANDEMİR Nurgün, MD
KANRA Güler, MD
KANRA Tekin, MD
KARAGÖL Uğur, MD
KINIK Erol, MD
KİPER Nural, MD
KOÇAK Hulusi, MD
KOÇAK Nurten, MD
KÖLEMEN Fikret, MD
KUTLUK Tezer, MD
MISIRLIGİL Zeynep, MD
MUŞDAL Yaser, MD
OĞUZ Aynur, MD
ÖZALP İmran, MD
ÖZÇELİK Tayfun, MD
ÖZÇELİK Uğur, MD
ÖZEN Hasan, MD
ÖZEN Seza, MD
ÖZER Sema, MD
ÖZGÜÇ Meral, PhD
ÖZKUTLU Süheyla, MD
ÖZME Şencan, MD
ÖZSOYLU Şinasi, MD
SAATÇİ Işıl, MD
SANAÇ Ali Şefik, MD
SARAÇLAR Muhsin, MD
SERDAROĞLU Ayşe, MD
ŞENOCAK M. Emin, MD
TANYEL F. Cahit, MD
TAŞER Ferda, Dt
TEKİNALP Gülsevin, MD
TECAN İlhan, MD
TOPALOĞLU Haluk, MD
TOPALOĞLU Rezan, MD
TUNCER A. Murat, MD
TUNÇBİLEK Ergül, MD
YALAZ Kalbiye, MD
YETGİN Sevgi, MD
YURDAKÖK Murat, MD
YURDAKUL Yurdakul, MD
YÜCE Aysel, MD

ANNOUNCEMENTS

TAIPEI, 26-30 MARCH 2000
10th ASIAN CONGRESS OF PEDIATRICS
Inquiries to : 10th ACP Secretariat
6F, 400, Kee Lung Rd., Sec. 1
Taipei 110
TAIWAN
Phone : 886-2-2722-1227
Fax : 886-2-2723-4187
e-mail : pcogis@ms14.hinet.net
website: http://www.pcogis.com.tw

ANTALYA, 26-30 MARCH 2000
10th NATIONAL NEONATOLOGY CONGRESS
Inquiries to : Valör Tourism and Travel Agency
Portakalçiçeği Sokak, No: 2/7
06590 A.Ayrancı
Ankara
TURKEY
Phone: (0312) 440 24 90 or
447 46 07 or 440 97 58
440 97 59
Fax : (0312) 447 46 10

JERUSALEM 10-14 APRIL 2000
THE SECOND INTERNATIONAL CONGRESS ON PEDIATRICS IN THE COMMUNITY (SIPCC) 2000
Inquiries to : Congress Secretariat
ORTRA Ltd.
1 Nirim St.
PO Box 9352
Tel Aviv 61092
ISRAEL
Phone : +972 3 638 4444
Fax : +972 3 638 4445
e-mail : pediat@ortra.co.il
website: www.ortra.com/pediatrics

ANKARA, 12-15 APRIL 2000
IIIrd INTERNATIONAL CONGRESS OF NUTRITION AND DIETETICS
Inquiries to : Flap Tour
Cinnah Caddesi, No: 42
06690 Çankaya
Ankara
TURKEY
Phone : +90 (312) 442 07 00
+90 (312) 438 21 21-22-23
Fax : +90 (312) 440 77 99
e-mail : flaptour@flaptour.com.tr
website: www.flaptour.com.tr

İZMİR, 20-22 APRIL 2000
FIRST WORLD CONGRESS OF PEDIATRIC THORACIC DISCIPLINES
Inquiries to : Prof. Oktay Mutaf
Ege University
Faculty of Medicine
Department of Pediatric Surgery
35100 Bornovo
İzmir
TURKEY
Fax : +90 232 375 12 88
e-mail: omutaf@med.ege.edu.tr

İZMİR, 26-29 APRIL 2000
ADOLESCENT AND YOUNG ADULT TUMORS
Inquiries to : Funda Çorapçıoğlu
Dokuz Eylül University
Institute of Oncology
35430 İnciraltı
İzmir
TURKEY
Phone : +90 (232) 277 96 66
Fax : +90 (232) 277 96 55
e-mail : fundacp@cs.med.deu.edu.tr
website: turkpog.kongresi.gne.tr

ANTALYA, 3-7 MAY 2000
FAMILIAL MEDITERRANEAN FEVER
IInd INTERNATIONAL CONFERENCE
Inquiries to : Figür Turizm ve Organizasyon Ltd.
Nişantaşı Ihlamur Yolu
Yonca Apt. No: 40/3
80200 Topağacı
İstanbul
TURKEY
Phone: +90 (212) 232 52 19
Fax : +90 (212) 231 12 62
246 18 69
e-mail: figumorth@ticaretnet.com

ANKARA, 14-16 MAY 2000
IInd NATIONAL CONGRESS OF PEDIATRIC NEUROLOGY
Inquiries to : Congress Secretariat
Hacettepe University
Faculty of Medicine
Department of Pediatrics
Neurology Unit
06100 Hacettepe
Ankara
TURKEY
Phone: +90 312 311 37 11 or
305 11 65
Fax : +90 312 311 62 62
e-mail: mtopcu@gen.hun.edu.tr

İSTANBUL, 29 MAY - 2 JUNE 2000
XXXVIth TURKISH PEDIATRICS CONGRESS TURKISH PEDIATRICS AND OUR CHILDREN IN THE BEGINNING OF THE THIRD MILLENIUM

Inquiries to : Congress Secretariat
İstanbul University
Cerrahpaşa Faculty of Medicine
Department of Pediatrics
P.K. 2
34303 Cerrahpaşa
İstanbul
TURKEY
Phone: +90 (212) 530 03 31
Fax : +90 (212) 586 15 95
588 49 18

STOCKHOLM 4-6 JUNE 2000
XIIIth INTERNATIONAL CYSTIC FIBROSIS CONGRESS

Inquiries to : Congress Secretariat
Stockholm Convention Bureau
XIIIth International Cystic
Fibrosis Congress
P.O. Box 6911, SE-102 39
Stockholm
SWEDEN
Phone: +46 8 736 15 00
Fax : +46 8 34 84 41
e-mail: cf@stocon.se

BURSA, 4-8 SEPTEMBER 2000
44th NATIONAL PEDIATRIC CONGRESS WITH INTERNATIONAL PARTICIPATION CHILD HEALTH IN THE 2000s

Inquiries to : Prof. Dr. Nihat Sapan
Congress Secretariat
Milli Pediatri Derneği
Bursa Şubesi
Bursa
TURKEY
Phone: +90 224 442 85 62
Fax : +90 224 442 85 82
e-mail: nsapan@uludag.edu.tr

CAMBRIDGE, 13-17 SEPTEMBER 2000
VIIIth INTERNATIONAL CONGRESS OF INBORN ERRORS OF METABOLISM

Inquiries to : Congress Secretariat
VIII ICIEM
42 Dvonshire Road
Cambridge CB1 2BL
U.K.
Phone : +44 (1223) 323437
Fax : +44 (1223) 460396
e-mail : cc@confcon.demon.co.uk
website: www.ssiem.org.uk

PORTOROZ, 4-6 OCTOBER 2000
26th CONGRESS OF THE UNION OF MIDDLE EASTERN AND MEDITERRANEAN PEDIATRIC SOCIETIES (UMEMPS)

Inquiries to : UMEMPS
Dr. Ivan Vidmar
Klinicni oddelek za otrosko kirurgijo
in intenzivno terapijo
1525 Ljubljana
SLOVENIA
Phone: +368 61 130 17 14
Fax : +368 61 130 17 14
e-mail: Ivan.Vidman@kclj.si

NOTICE TO AUTHORS

The Turkish Journal of Pediatrics is an English publication of original articles, case reports, reviews of the literature, case of the month, short communications, clinicopathological exercises and letter to the editor in the field of pediatrics, and will consider papers from authors of all countries. Original articles should report scientific findings within the pediatric field of interest. Case reports should contain accounts of rare syndromes, new diagnostic tools and methods, new kinds of treatment and laboratory research with foreseeable practical application. Review articles should contain an objective account of different points of view and an internationally representative bibliography. Authors considering submission of review articles of medical progress are encouraged to consult with the Editor before submission. Papers should in general not exceed 15 written pages for original articles or 7 for case reports and reviews of the literature, including tables, figures and illustrations. All papers are subject to editorial revision for the purpose of conformity to the style adopted by *The Turkish Journal of Pediatrics*, and authors may be requested to shorten or revise their papers.

Statements and opinions expressed in the articles are those of the author(s) and not necessarily those of the Editor or publisher; the Editor and publisher disclaim any responsibility or liability for such material. Neither the Editor nor the publisher guarantees, warrants, or endorses any product or service advertised in this publication; neither do they guarantee any claim made by the manufacturer of such product or service.

We recommend that all manuscripts be approved for submission by the department chairman or head of the institution in which the study has been done. All manuscripts must be accompanied by the following **written statement,** signed by the author(s): "The author(s) transfer(s) all copyright ownership of the manuscript entitled (title of article) to *The Turkish Journal of Pediatrics* in the event the work is buplished. The author(s) warrant(s) that the article is original, is not for consideration by another journal, has not been previously published (except in a congress report), and has been prepared according to the manuscript rules" (as described below). Papers describing research involving human subjects should indicate that informed consent was obtained from the parents or guardians of the children who served as subjects and, when appropriate, from the subjects themselves.

Preparation of Manuscript

Contributors are requested to pay particular attention to the following rules governing the preparation of manuscripts. Failure to follow these rules is a frequent cause of delay in the publication of articles and may result in rejection of otherwise acceptable manuscripts. Manuscripts should be sent in triplicate (original and two photocopies acceptable) to the Editorial Secretary, *Turkish Journal of Pediatrics,* P.K. 66, 06240 Samanpazarı, Ankara, Turkey. Manuscripts, whether rejected or published, are not returned to the authors, but original illustrations which are rejected are returned upon request of the author.

Format Manuscripts should be typed, double-spaced, on one side of the paper only, with wide margins.

Title Page A separate title page should include authors' names and academic degrees; departmental and institutional affiliations of each author, and sources of financial assistance, if any. Designate one author as the correspondent, and provide an address as well as business and home telephone numbers. Galley proofs and order forms for reprints will be sent to the corresponding author, at a later date.

Contents Each original article should contain the following sections: Introduction, Material and Methods, Results, Discussion and Summary, and each Case Report should contain an Introduction, Case Report, Discussion and Summary.

Abbreviations Abbreviations must conform to accepted standards. Laboratory slang, clinical jargon and colloquialisms must be avoided.

Tables Tables should be numbered with Roman numerals according to the order of mention in the text. Each table must be typed double-spaced on a separate sheet of paper, and a concise title supplied for each. Tables should be self-explanatory and supplement, not duplicate the text. If a table or any data therein have been previously published, a footnote must give full credit to the original source.

Figures Figures and illustrations should be of direct interest to the subject of the paper and numbered with Arabic numerals according to order of reference in the text. Figures should be drawn on white paper and photographs must be clear prints. The name of the first author and the number of the figure or illustration must be written in pencil on the back of each, with an arrow indicating the top side. Original drawings or graphs should be prepared in black India ink or typographic (press-apply) lettering. Typewritten or freehand lettering is unacceptable. All lettering must be professional and in proportion to the drawing, graph, or photograph. Do not send original art work, x-ray films or ECG strips. A list of legends for the figures and illustrations must be provided on a separate page.

Summary / Abstract An informative summary not exceeding 150 words must accompany each manuscript, typed on a separate sheet. Unexplained abbreviations and references are not allowed.

References References to the literature should be limited to those cited by the author, arranged and numbered according to order of mention in the text. All authors of an article or book should be listed where there are six or fewer. If more than six, the first three names should be given followed by the indication "et al". In a manuscript underlining indicates italics.

References to journal articles:

Example : 1. Bier DM, Fulginiti VA, Garfunkel JM, et al. Duplicate publication and related problems. Pediatrics 1990; 86: 997-998.

Names of journals are to be abbreviated in accordance with the style of *Index Medicus.*

References to books:

Example : 2. Praat RTC. *The Genetics of Neurological Disorders.* London: Oxford University Press; 1967: 173-174.

References to chapters in books:

Example : 3. Kissane JM. Development of the kidney and congenital malformations. In: Heptinstall RH (ed). Pathology of the Kidney (2nd ed) Vol. 1. Boston: Little, Brown and Co; 1974: 69-109.

Key Words Authors are requested to list on a separate sheet of paper key words related to their article. These will bu used in compiling an index for the volume of the journal in which the article appears.

Proofs and Reprints Galley proofs will be sent to the corresponding (or principal) author by the editor. The master proof should be returned to the Managing Editor together with the manuscript within two days, and by air mail if received by air mail.

Announcements Announcements of scheduled meetings, symposia, or postgraduate courses may be sent to the publisher for consideration at least 5 months in advance of the meeting date.

Books for Review Books and monographs, domestic or foreign, may be sent to the Editor for consideration for review. No books are returned, nor acknowledgement made of books received.

Advertising Communications of a business nature and all advertising communications should be addressed to the Journal's Editor.

Checklist

Please check your article as described below before sending it to the Editor.

- Letter of submission
- Signed "Statement" (which is written on a separate paper) as described above
- Three copies of article (one original and two photocopies will be acceptable).
- Title page
  - Title of article
  - Short running title
  - Name(s), academic degrees, and affiliations of author(s)
  - Name, address, and business and home telephone numbers of corresponding author
- Article proper
  - Original articles: Introduction, Material and Methods, Results, Discussion, Summary
  - Case Reports: Introduction, Case Report, Discussion, Summary
  - Key words
- References on a separate sheet
- Tables on separate sheets
- Legends on separate sheets
- Illustrations properly labelled (one set of glossy prints and one set of photocopies).